LECTURES
ON
SURGICAL PATHOLOGY.

PARK.

THE MÜTTER LECTURES

ON

SURGICAL PATHOLOGY.

Delivered Before the College of Physicians of Philadelphia,

1890-91.

BY

ROSWELL PARK, A.M., M.D.,

PROFESSOR OF SURGERY, MEDICAL DEPARTMENT, UNIVERSITY OF BUFFALO;
SURGEON TO THE BUFFALO GENERAL HOSPITAL; FELLOW OF THE
GERMAN CONGRESS OF SURGEONS, ETC.

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PREFACE.

By the will of Prof. T. D. Mütter, The College of Physicians of Philadelphia was, a number of years ago, enabled to establish a triennial course of lectures on topics connected with surgical pathology, the lecturer being required to deliver not less than ten in the course. The following lectures comprise those delivered, in compliance with his bequest, during the season of 1890–91.

In the selection of subjects no attempt has been made to follow a systematic outline of all that properly may be included under the term surgical pathology. To attempt this in ten lectures would have been folly. The effort has rather been either to deal with the newest phases of old and familiar doctrines, or to consider certain subjects not dealt with in works readily accessible to the general practitioner.

In their selection the writer has simply followed his own notions of their importance or of his own facility for dealing with them; and for them, as for personal views expressed, he is solely responsible. He has not hesitated to avail himself of all current literature at command, and has endeavored to give credit to all to whom it is due. Any failure in this respect is one of unintentional oversight.

Much of what has been gleaned from the writings of others has never before been presented in English dress, and the hope is ventured that the following pages may, on this account, be accorded a value which such original views or investigations as they may set forth might not confer.

510 Delaware Ave., Buffalo, N. Y., December, 1891.

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THE MÜTTER LECTURES ON SELECTED TOPICS IN SURGICAL PATHOLOGY.

SERIES OF 1890-1.[1]

By ROSWELL PARK, A.M., M.D.,

OF BUFFALO,

PROFESSOR OF SURGERY, MEDICAL DEPARTMENT, UNIVERSITY OF BUFFALO; SURGEON TO THE BUFFALO GENERAL HOSPITAL, ETC.

LECTURE I.

INTRODUCTION.—*Ever-growing importance of the study of Surgical Pathology. Lessons to be learned from the life-work of eminent observers.*

The inflammatory process: its varieties. Granulomatous inflammation. Thrombi; varieties and how formed. Traumatic anæmia. Hæmoglobin and oligochromæmia. Aerobic and anaerobic life of the organism, and chemical products of the same. Ptomaines and leucomaines; classification and definition of same. Toxines. Proof of formation of ptomaines by bacterial action.

Classification of infectious diseases. Surgical infections and discussion of conditions predisposing to them. Embolism as one of these conditions. General depression of vitality. Local depression. Influence of inflammation; of cold; of injury.

IT WILL not be amiss if at the opening of the present course, the lecturer prefaces its more technical portion with a few words concerning the present advanced stage of surgical progress, and the causes which have contributed thereto. If we call before our minds the really great surgeons of to-day, or of the present generation, and ask ourselves by virtue of what particular attributes they have become great, we shall satisfy ourselves that they are not only good anatomists, and men of broad general attainments, not only are they all—or nearly all—brilliant operators; but more, much more than this, they are all good physiologists, and especially, good *pathologists*.

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[1] Delivered before the College of Physicians, Philadelphia, December, 1890.

Sound and tenable pathology is to-day as essential for the surgeon as for the physician; one needs it as much as the other. If at this time there is any one respect in which the continental surgeons eclipse those of our country, it is in this. Better anatomists they are not—certainly not better operators—for the most part not as good. But by virtue of their early training, and by the influence of tradition and surrounding, they are reared in an atmosphere—so to speak—of pathological interest and lore; they imbibe it as part of their daily increment of knowledge, and hence they acquire whatever element of superiority they may enjoy over their American *confreres*. It is hardly my business, nor is it my purpose here to try to point out the reasons for this state of affairs, nor to suggest remedies.

But I can do no greater service to the younger men to whose notice these words may come than by every means, and by every argument in my power, impressing and insisting upon their conviction that the early years of their medical studies constitute the golden opportunity for laying in that store of elementary knowledge of normal and morbid physiology, *i. e.*, pathology, and of that familiarity with instruments of research and of technical methods, which shall prove of inestimable advantage to them a little later. How many men whom we could name at once have fallen just short of greatness because of deficiency in this respect! And what a magnificent future lies before succeeding generations of surgeons, if they will but properly prepare themselves for it!

Langenbeck, who well deserved the proud title of Nestor of recent German surgeons, did no greater service for surgery than when he brought to his professional surgical chair the practical knowledge of physiology which he had acquired by teaching it, and introduced into his akiurgical instruction the experimental method as the two never had been combined before. By this method, as it was practiced by him and his pupils, there was brought about almost a second *renaissance* of surgery; while its conspicuous advantages turned the tide of surgical travelers from London and Paris toward Germany, and put German teaching—of this branch of the healing art—so far ahead that even to-day those who would not go to Germany have no need to leave this country for the acquisition of such knowledge. Outside of Germany the same is true in little less noticeable degree. The two London surgeons, most honored of all, at home and abroad, are Sir James Paget and Mr. Jonathan Hutchinson; and of the French no man's opinion carries more weight than does that of Verneuil or of Ollier. Yet if I were asked whether these men rank higher as surgeons or as pathologists, I should unhesitatingly say as the latter. And no better illustration of the soundness of my position did America ever afford than was furnished here in your own city by the distinguished Gross. No one at all familiar with his life and work can deny that his greatness and his accuracy as a surgeon were in very large measure due to the attention he paid to pathology during his early years, or indeed all his life. A cursory examination of his early text-book on this subject will be convincing in this respect.

Aside from the ordinary knowledge and ability, which, by common consent, every surgeon deserving the name should possess, it seems to me that the cultus of the day demands that hereafter none should be deemed competent to practice surgery who have not had competent and abundant training along the lines of

1. Experimental physiology and pathology.
2. Pathological histology and general pathology, including
3. Bacteriology.

It cannot be considered as improper or too personal if I mention a few individuals among living surgeons, whose work illustrates forcibly the advantage of such training. I know of no one who has more happily combined the dexterity of the accomplished surgeon with the training and education of the expert physiologist than Mr. Victor Horsley. As first an assistant to Prof. Burdon Sanderson, he acquired that familiarity with the endurance of living tissues, and the minute functions of the various organs, which has enabled him to make his operations upon the human patient the marvel and the admiration of contemporary surgeons. So with the leader of the

Austrian surgeons, Billroth, and notably with his best known pupils, like Czerny, Gussenbauer, Wölfler and others. So too in the highest degree with that great Lyons master of bone-surgery, Ollier, whose volumes bristle with facts attesting his devotion to the experimental method.

Among living surgeon-histologists no names better deserve mention perhaps than those of Paget, of Lannelongue and Butlin. Volkmann led here, as he did in every other department, and, though now he rests from his labors, is entitled to be named with the others who were his contemporaries.

Of surgeon bacteriologists perhaps the best known are Rosenbach and Fehleisen, though Cheyne and Neisser, with others equally deserving, are scarcely less known.

Nor must we forget what home surgeons are doing in these various fields, for such names as those of Parkes, Senn, Halstead and Warren must be written in large letters on this particular tablet of surgical history.

Pathology, then, is a *sine qua non* for the modern surgeon, and everything which fosters fondness for, and familiarity with, it should meet with hearty encouragement. To this end it must assume an ever-increasing importance in every college curriculum, and to this end also every such collection as the invaluable one which this college contains should be daily haunted, and no opportunity of securing and preparing specimens for private or public collections should be neglected. Above all things, the many opportunities for study of comparative pathology, both natural and experimental, which are constantly afforded, both in city and country, should be utilized to the fullest possible extent.

The most brilliant illustration of what such study may do for one is afforded in the person of Mr. J. Bland Sutton, who stands to-day a young man, yet one of the most prominent figures, in my estimation, among pathologists, living or dead; who has made thousands of autopsies upon animals, the number including nearly every known genus, who has contributed to the magnificent collection of the Royal College of Surgeons some of its most valuable specimens, and who in tastes and acquirements well deserves to be considered the legitimate successor of John Hunter. He, practising and now working as a surgeon, has, nevertheless, almost created the science of comparative pathology; and it is to be earnestly hoped that he may be induced to undertake a systematic treatise upon this subject—which as yet does not exist in any language. Of the value—surgical and pathological—of his writings, only those can speak who have read them, as all ought to have done. I think he will pardon me if I place his career before you as one which is deserving alike of greatest praise and closest possible imitation.

To this end, also, the founder of this course of lectures, with that wisdom and foresight for which he was so distinguished, ordained that they should be devoted to topics connected with surgical pathology. Although the field is immense, the number of laborers in it is correspondingly large, and it has been my aim less to intrude upon you personal views and experiences, or statements of personal work, than to collate and compare the results of investigators the world over, and to invite your attention to the present state of knowledge concerning some of the most contested or most important and interesting topics to-day discussed or considered by the surgical profession.

I have in my library an interleaved copy of a "Syllabus of the Course of Lectures on the Principles and Practice of Surgery, Delivered in the Jefferson Medical College," by Thomas D. Mütter, M.D., published in 1847, with copious notes, interlineations and annotations by Prof. Howard Rand. I have been much interested in looking over the note headings to see the extent of its author's erudition in the surgical pathology of his day, and the attention which he compelled his students to devote to it, and have often thought how well it would be if some of the surgical teachers of to-day would more closely imitate him in this respect. To be sure, there is much therein which needs elision, revision or contradiction, such as the statement on page 10, that suppuration can occur in 35 minutes; yet the whole syllabus so clearly indicates the character of his teaching and his bent of thought, that one scarcely wonders at the general drift which he so wisely insisted this course of lectures should assume.

Inasmuch, therefore, as all pathological processes begin with alteration of nutrition, of cell activity and of the constitution of the vital fluids, it has seemed wise to first discuss a few of the more important of these changes in the light of recent studies; in other words, to begin in our studies of surgical disease where nature appears to begin in its production.

The inflammatory process is modified according to conditions of environment and cause, and may be classified under four different headings—as regenerative, productive, exudative and destructive. The *regenerative* form especially concerns the surgeon in the matter of healing of wounds. It is always followed in every case, and in whatever disease, by cicatrization. *Productive* inflammation is met with after injuries or destruction of particular tissues; is at times adhesive, at times hyperplastic. *Exudative* inflammation is serous, sero-fibrinous and sero-hæmorrhagic. *Destructive* inflammation is either suppurative or gangrenous, or both. To these four forms might perhaps be added a fifth, the *granulomatous* inflammation, of which we shall later speak more at length.

To the serous form of exudative inflammation there has been given the name of inflammatory œdema. This must be sharply distinguished from those forms of œdema which are due to mechanical disturbances of the circulation. When the blood stream is interfered with in the veins, while the arterial stream is circulating in full force, there must occur stasis in the capillary veins. Under these circumstances serum is forced through the distended vessels and into the tissues, and there fills the intercellular spaces and minute canals. This form of œdema is as different from inflammatory as is blood serum from blood. In the mechanical form the serum is poor in fibrin, while in the inflammatory form it contains not only fibrin, but the other elements of the blood. Serous inflammations of higher grade which contain a relatively large percentage of fibrin are known as sero-fibrinous. The flocculent precipitate of fibrin is produced by a mutual reaction of fibrinogin and fibrino-plastin, just as they produce blood clot under other circumstances. In rare cases there is added to the exudate of serous inflammation the red blood corpuscle element. When this is in excess it is known sometimes as hæmorrhage by diapedesis. The ordinary termination of exudative inflammation is a complete return to the normal standard. In a small proportion of cases, especially involving serous cavities, there remains a portion of the exudate, which predisposes the part to a recurrence of the trouble.

Rapid progressive inflammation leads not infrequently to stasis and to coagulation of the blood in surrounding tissues or in the smaller arteries. If now the collateral circulation is sufficient resorption is still possible; if not, local gangrene is the result. Around the margin of such a gangrenous focus there will always be a zone of suppuration which may be taken as an instance of *pyo-gangrenous* inflammation. It is not necessary to have inflammation of the highest grade in order to produce gangrene; it is frequently enough to have the supply of nutritive material shut off. Thus one sees often, even in a simple case of this kind, considerable portions of tendon slough off, since the tendon contains no blood vessels, but only canals through which nutrition is furnished by osmosis. Should such an inflammation progress to the neighboring muscles, it loses its gangrenous character in all probability, since here blood vessels supply the proper nourishment. For gangrene of muscles ordinarily, the highest grade of diphtheritic inflammation is necessary.

Granulomatous inflammations.—These are always chronic processes. One sees them confined almost to individuals of peculiar constitutional condition, such as are usually grouped under the head of the scrofulous, the syphilitic or the leprous. In contra-distinction to the serous and purulent forms of inflammation, these have little or nothing to do with skin lesions or access of air to the tissues. They are produced rather without injuries, and in those cases in which injury is alleged, it is usually of the nature of a deeper crushing without cutaneous lesion. Most of these cases pertain to the period of youth. Most commonly the bone marrow is involved, and it seems as if the marrow of growing bone were peculiarly liable to this affection. Still, granulomatous inflammation of the skin is common, as well as in joint cavities. If we examine a piece of tissue from the beginning of a granulomatous inflammation macroscopically and microscopically, and compare it with a small fragment from a case of purulent inflammation, we shall not find any marked difference; both consist of new blood vessels with heaps of small round cells between them. In their further course;however, the difference notably increases. The granulation tissue in the neighborhood of the acute abscess is a great help to its subsequent healing. In the other case, however, the cells break down after infection, and form small abscesses which frequently coalesce, and these form others of considerable size, which pursue the well known course of the sub-acute or cold forms. As the result of spontaneous perforation of these latter we have granulating ulcers and fistulous passages of an ulcerative character, which may lead deeply, even down to the bone marrow. The significant feature of granulomatous inflammation is, that it never tends to formation of a firm cicatrix or healing; it tends to remain indolent, or to become more and more destructive. Its destructive products are never natural pus; they contain fragments which have a caseous appearance, and they lead to so-called caseous degeneration, or, through fatty degeneration, we may meet with veritable fat balls in its substance. There occurs a complete transformation of albuminoid, nitrogenous substances, into those which are fatty and free from nitrogen.

Any synopsis of the forms of inflammation leads by a path which cannot be avoided to the topic of thrombi and thrombosis, and indeed the question of the formation of thrombi is one of such universal interest, since thrombi have so much to do with surgical diseases, that it will be well to stop to consider briefly how, and under what circumstances, they are most often formed. The first variety of which we shall speak, following Klebs, is the coagulation of fibrinous form, the second that which is formed from red cells and globulin; the third that from leucocytes; yet another is formed from hæmatocytes, and a fifth is produced through the instrumentality of the hæmatoblasts, or the third corpuscular element of the blood. Each of these forms may be met with by itself, but mainly we have to deal with mixed thrombi.

A. *Fibrinous thrombi.*—Fibrin is the principal material out of which these are formed, and this possesses the property of adhering to the vascular wall, which naturally appears to be the first requisite of thrombus formation. This is the form which most commonly gives rise to secondary thrombosis or embolism. The cases in which a simple separation of fibrin from the circulating blood occurs by itself are rare; some foreign body in the circulation is usually the prime cause. A roughness of vascular surface has been supposed to be sufficient to favor coagulation of the fibrin, but the condition of atheroma of the vessels, by which their interior is roughened, does not lead to thrombosis as often as would be expected. The death of the vascular wall, whose life is an important cause of the fluidity of the blood, does not invariably lead to thrombosis, as the uncovered calcareous plates of the interior of the vessels will prove. Even cauterization of limited areas of vessel walls does not necessarily always produce thrombosis; neither does ligature of vessels. On the other hand when fibrin ferment is introduced into the circulation, or when the same is set free in the blood, as may be done by injections of ether, we have most extensive thrombus formation. This naturally raises the question whether such a thing can occur under natural conditions, and this has hardly yet been answered definitely. The thrombi which form in the heart during the last moments of life can hardly be considered to have formed under natural conditions. There is considerable reason to think that in septic conditions the fibrin ferment of the patient's blood is altered in amount or activity.

B. *Hæmatoblastic or globulin thrombi.*—The third corpuscular element of the blood is now well known, although whether it be a normal constituent, or an intermediate or retrograde form, is hardly yet decided. Without discussing to any extent the conditions under which thrombi are produced by the action of these corpuscles, we have to side either with those who consider them to be normal blood elements, and recognize under what pathological or physiological conditions they increase, or else we must deny that they are normally present. Hayem found a significant increase after ingestion of food, but in pathological conditions different observers have obtained so widely varying results that it is impossible, as yet, to assign to them any distinct role. Here, again, we must allude to the fact that the cauterization of areas of vascular walls does not necessarily lead to thrombosis, with the exception of those points at which a loosening of the cauterized scale leads to some unevenness of the surface. Even at these points it does not always occur. Evidently then when thrombosis does here occur, some condition not obtaining in the vessel wall itself must lead to it. Perhaps the rapidity of the blood stream has much to do with it; but more important, probably, is the part played by this third corpuscular element. It has hitherto been very difficult to experiment with this, since the conditions of the experiment inevitably lead to inflammation of the areas under observation. However, Lowit has recently succeeded in examining the mesentery of mice under castor oil, by which no inflammation is produced, and by means of which he was able to convince himself of the absence of hæmatoblasts at points where the circulation was slackened. Slight cauterizations of the vessels with points of nitrate of silver produced hæmatoblastic thrombi, which contained leucocytes, and which broke loose and were rapidly reformed at the same points; and he was even able to observe the breaking down or disintegration of the stagnant, red corpuscles. The leucocytes also broke up, after a time, as Zahn has already described.

C. *White or leucocyte thrombi.*—These were long ago recognized by Virchow as a separation of the white corpuscles, which earlier authors had held to be pus corpuscles,taking place where a slowing of the circulation leads to thrombosis. In such cases,as Cohnheim showed,the white corpuscles leave the more rapid central stream,and attach themselves to the surface of the vessel wall, especially at those points where circumstances favor, as the point of division of the vessel, or where a sudden curve or dilatation leads to stagnation of the current. Other favoring circumstances are changes in the intima, such as roughening or minute alterations of the endothelium by which exudation is more easily permitted. Thrombi formed by leucocytes alone are relatively rare, a leucocyte immigration into a fibrinous thrombus naturally being included under this term. They are most common in cases of leucæmia in which the capillaries of the mucous membranes, especially of the intestines and nose, are filled with them and made to resemble white streaks. They occur also in the rear of some emboli when the section of the occluded vessel behind them is very short;

also behind venous valves and in the spaces between the bundles of muscle fibres in the heart, and in the sheltered cavities which form in connection with aneurisms and varices. They may also form in slowly circulating blood as free thrombi.

D. *Red blood corpuscle or hœmatocyte thrombi.*—Constituted primarily from adhesion of the red corpuscles. This is a genuine stagnation form. Aside from stagnation, a second condition, namely the removal of the blood plasma from the stagnant blood mass, is a contributing feature. It takes place also when pressure is exercised upon the red corpuscles. White corpuscles which are entangled with the red are usually destroyed or lose their identity. The pure stagnation thrombi are usually formed at those points where a good-sized vascular area is shut out, as for example, after the ligature of a vein of some size. Under these circumstances the arteries are dilated and the collateral circulation easily takes off the overflow. All so-called ischæmic conditions, depending upon arterial contraction, can cause stagnation thrombi if they occur in a region whose veins are enlarged and filled with plenty of blood. The essential condition of the stagnation thrombus, the lessening of venous flow, is always accompanied by an increase of pressure in the capillaries and veins, and it is this which determines an increase of exudation, and this in turn leads to a typical œdema. General or partial venous stasis furnishes all the necessary requirements for the formation of hæmatocyte thrombi. Very typical forms of these are met with in senile gangrene; so also contusions and inflammations of injured portions produce the same effect. Especially unfavorable is the extension of inflammatory processes along the arteries, by which are produced extensions of thrombi, mostly in the shape of fibrinous additions. A marked instance of these thrombi is met with often in the so-called arterio-venous aneurism, that is, the traumatic communication between an artery and a vein. There belong also in this category a large number of divers forms resulting from venous stasis combined with hæmorrhage, such, for instance, as occur about the constriction in a case of strangulated hernia. Such conditions lead frequently to so-called hæmorrhagic gangrene. So far as the future of these thrombi is concerned it is not necessarily unfavorable so long as further changes in an undesirable direction do not occur, since with improvement of the circulation compensatory and absorbtive processes are instituted; but if they exist too long there occur changes in the character of organization, or, if infected, in a destructive direction.

E. *The mixed or the thrombus in layers.*—These layers, as is well known, are formed by deposition at different times of the solid material of the blood, this material being now of one of the above forms, at other times of another. The surgeon meets with this variety most commonly in dealing with aneurisms or hæmatomata, in which concentric deposits from contained fluid have taken place. In another signification the mixed forms are met with often in those thrombi which obliterate vessels.

As appears above, explanation of some of these forms of thrombus-formation is simple, at other times it is difficult, or as yet impossible. Remembering how rapidly blood coagulates outside the body, remembering, too, what differences may be observed, in this respect, in the blood of different patients, it will be seen that it can scarcely be expected of us to imitate outside of the living body the conditions existing within it, nor to solve all the problems of vital chemistry.

Nevertheless, a distinct advance has been made, first in the ecognition, and then the accurate study of ptomaines and leucomaines, and there is now every reason to think—nay, to state with little or no reserve, that there often takes place a form of ptomaine or leucomaine intoxication, analogous to that produced experimentally by certain substances, such as the fibrin ferment; and that under these circumstances there may occur an almost instantaneous and extensive thrombosis, or analogous change, wherever the poison reaches. Surely in this way are we to account for the altered quality of the blood so universally recognized and commented on as among the changes during and after death from the various infectious diseases. So large a part in the pathology of the blood is now borne by these alkaloid substances and toxines that to them we must presently devote some attention.

But, dealing still with the blood and its natural constituents, for a few moments, let us see what recent research has shown us concerning blood loss, and how it is atoned for.

In cases of traumatic anæmia there is a relative or rather an absolute *decrease* of leucocytes. Ehrlich has shown that 80% of white corpuscles are formed from lymphocytes, while the balance are represented by multinuclear neutrophile, or mononuclear neutrophile cells and transition forms, in the proportion of 14, 3, and 3%. His eosinophile cells are formed solely and normally from bone marrow. The decrease in number of leucocytes in traumatic anæmia is due to failure of equilibrium between the true lymphatic structures on the one hand and the spurious, like the spleen and the bone marrow, on the other. Cohnheim some time since showed how in cases of acute anæmia following injury the bone marrow tends to revert to the embryonic condition, and its failure to produce these cells may, perhaps, be explained in this way. They constitute a definite constituent of normal blood, and are found in proportion of 2 to 4%, which may even increase to 10%. Their complete absence, therefore, points to a disturbance of function, at least in bone marrow.

As a matter of common interest we may add here that the character of a given case of anæmia may be largely determined by a study of the red corpuscles. In all severe forms nucleated red cells are found, which bespeak an active regenerative process. In secondary anæmias these nucleated corpuscles have normal size, and may be called normo-blasts; while in the pernicious forms they have a much larger size, corresponding to embryonal types, and may be called giganto blasts. This method of differential diagnosis is, indeed, recommended by Ehrlich as the safest of all.[1] Possibly this fact also finds its explanation in the above-mentioned discovery of Cohnheim.

Hæmoglobin. That the amount of hæmoglobin in the blood varies within wide limits under different conditions has been known for some time, yet it is only recently that a careful study of the amount present in various surgical diseases has been determined. At the Congress of German Surgeons of 1890, Mikulicz presented the results of a study of some 400 cases, mostly operative. Two questions especially concerned him. First, in what time after serious loss of blood in man does regeneration occur, and what influences thereupon have age and sex; second, in relation to those diseases which we are inclined to associate with a vitiated constitution, what striking variations have we in the amount of hæmoglobin in the blood, and its regeneration after hæmorrhage? The first question has been studied in animals from many sides, but only a few observations have been made in man. Concerning the second question, Leichtenstern and Laker have offered some interesting observations, but only in relation to tuberculosis. Mikulicz perceived during the examinatson that the estimation of the actual blood loss depended on manifold factors. In the case of each disease the amount of hæmoglobin had been determined before the operation as well as afterward at stated intervals, say at two or three days. The amount of the loss of blood found expression in the percentage determined from the original amount of hæmoglobin in the blood, while the gradual increase of the latter explains the augmented blood regeneration.

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[1] By far the best method of examining these various blood-cells is that known as Ehrlich's double-staining, the aniline dyes employed consisting of acid fuchsin, methyl green and orange green.

The estimation of the hæmoglobin was made by Fleischl's hæmometer. This instrument is easily handled, and permits an estimation in from three to five minutes. Personal equation produces error of from 2% to 5%. The subjoined table gives a summary of the amount of hæmoglobin and of blood regeneration, that is restoration to previous or normal standard, with reference to sex and age. It was made up from observation of one hundred and seventy-five patients who presented no so-called constitutional disease.

The ideal normal standard of 100% was discovered with Fleischl's instrument only in a few individual instances of strong young men in the third decade of life. The general average is considerably lower, the highest average appeared in men in the third decade of life, viz., 92%. This may be partly explained by the fact that persons presenting at a public clinic are scarcely to be considered as highest types of their class.

The female sex shows a smaller amount of hæmoglobin in the blood than the male. The different averages given here—about agree with the tables of Sterling, viz., males, 87.8, females, 84.5.

TABLE I.—THE AMOUNT OF HÆMOGLOBIN AND BLOOD REGENERATION WITH RESPECT TO AGE AND SEX.

Age.	Amount of Hæmoglobin.			Blood Regeneration.		
	Males and Females.	*Males.*	*Females.*	*Males and Females*	*Males.*	*Females.*
	Per cent.	Per cent.	Per cent.	Days.	Days.	Days.
1–10 years........	73.8	74	73	22.4	20	25.5
10–20 years........	82	83	81	17	15	18.5
20-30 years........	88.7	92	80.7	11.6	10.6	17.7
30–40 years........	84	88	76.6	12.5	11	14
40-50 years........	82	84	78	18	14	2
50–60 years........	84.8	88.6	79	20.6	18	24
60 and above......	83	85	78	25	24.5	29
Average.......	81.6	83	78	17	15.6	20.4

Sterling's examinations were made with Gower's instrument which gives a higher value than does that of Fleischl. Some striking differences appeared in reference to the speed of regeneration of lost hæmoglobin. The most rapid occurs in the third or fourth decades of life, it being much lower with children and the aged. This corresponds with the clinical experience that the very young or old bear loss of blood more poorly than do those of middle age. It also appears that females are considerably behind males in the same respects. With women in the third decade of life the average time of regeneration of 14.7 days agrees well with the observations on puerperal patients by Meyer, who observed within 14 days a permanent and complete restoration of the normal standard. The amount of blood lost also influences the result. Blood-loss which was indicated by 15% loss of hæmoglobin was, on the average, atoned for in 14 days, by 20% blood loss in 20 days, by 25% blood loss in 21 days, and all proportions over 25% of blood loss required on an average 29 days for restoration.

The minimum proportion of hæmoglobin reappears first after several days, quite in conformity with observations on animals. The greater the amount of blood lost, the later appears this minimum. When the blood-loss is up to 15%, this time is three and one-half days; with blood losses over 25% it averages nearly ten. The greatest loss of hæmoglobin appeared in a woman who had undergone extirpation from the abdominal wall of a large fibroma weighing some 30 pounds. Her proportion of hæmoglobin sank from 70% to 22%.

Regarding the largest losses of blood which men can stand, these appear to depend less upon actual loss of hæmoglobin than upon how much hæmoglobin still remains in the body. The minimum amount in a single patient after a major operation amounted to about 20%. In three cases dying of collapse this amount sank to about 15%.

Mikulicz believes that many of the cases dying on the second or third day after severe operation from so-called collapse are to be attributed to oligo-chromæmia, *i. e.*, deficiency of hæmoglobin in the blood. It is quite possible that an expert in these examinations might, from an estimation of hæmoglobin, give a reliable judgment as to whether in a given case the patient could or could not withstand a severe operation. In eleven cases estimations were undertaken just before and just after operating, in order to determine the effect of mental emotion, narcosis, etc. In every case there was found a loss of from 5% to 10%, from which it is easy to decide that chloroform narcosis exerts a decided influence upon the blood.

Table II gives a review of the amount of hæmoglobin and the regeneration period with different diseases which exercise more or less vital disturbance or which stand in causal relation with cachexia or dyscrasia. In seventy-nine cases of local tuberculosis where the hæmoglobin averaged 63% as against 81.6% normal, the period of regeneration was delayed at least a week. Delay was most conspicuous in cases of tubercular diseases of the lower extremities, least so with those of the soft parts. It is likely that every such lesion by which functional disturbances and impaired nutrition are caused must influence the condition of the blood. Laker also obtained similar results. The question whether tuberculosis as such influences the amount of hæmoglobin in the blood, or whether the

TABLE II.—THE AMOUNT OF HÆMOGLOBIN AND THE BLOOD REGENERATED WITH RESPECT TO CONSTITUTION.

Cases	*Disease.*	*Amount of Hæmoglobin before Operating.*	*Blood loss in per cent of the Hæmoglobin Reduction.*	*Regeneration.*
		Per cent.	Per cent.	Days.
1	Healthy......................	81.6	15.5	17
2	Tuberculosis:			
	a. Altogether......... ..	63	14.7	24
	b. Bone.................	....	15.5	....
	Lower extremity.........	60	15 5	26
	Soft parts................	70	13	17
3	Actinomycosis,...............	46	....	....
4	Syphilis, tertiary.............	55.4	15.4	18
5	Benign tumors:			
	a. Altogether.............	79	17.4	18.8
	b. Without complication.	83	15	16.8
	c. With rapid growth or of considerable size...	70	23.8	24.6
	d. With functional disturbances or putrefaction.	67.5	14.6	16.6
6	Malignant tumors:			
	a. Altogether............	60	17.2	26
	b. Without complication.	68.5	15.5	23
	c. With rapid growth or of considerable size...	56.6	18.2	27.8
	d. With functional disturbances or putrefaction.	57.6	17.8	27

descendant of a family characterized by a minimum of hæmoglobin is thereby predisposed to tuberculosis, cannot yet be answered from data at hand; but it is hardly likely. Certainly Mikulicz found that, in a series of cases, after complete healing of local tubercular trouble the amount of hæmoglobin rose far above the original height. On the contrary, in several cases in which the disease could be only incompletely removed, or where relapse occurred, the proportion of hæmoglobin did not attain the original height.

In ten patients with tertiary syphilis the amount was considerably reduced, though the regeneration period was uninterfered with. In four severe cases of actinomycosis the amount was still smaller. Finally, in thirty-two cases of benign, and seventy-two cases of malignant tumors, divided into three categories, *a*, uncomplicated tumors; *b*, those of rapid growth, of considerable size, or of severe hæmorrhages; *c*, those which were breaking down, or causing severe functional disturbances, as pressure upon the trachea or alimentary canal, the average amount of hæmoglobin in the benign tumors was reduced but very little from the normal; while in the first group the average was even higher than the normal, and in the second and third it was more or less reduced. The most striking reduction was in a case of large goitre causing severe compression of the trachea. In malignant tumors the average is reduced to about 60%. The statistics of Mikulicz concerning cases of mammary cancer, agree with those of Schmidt, of Heidelberg, who estimated it at from 50% to 60%. In malignant cases also the period of complete regeneration is materially retarded. Furthermore it was found that incomplete removal or recurrence prevented a typical regeneration or restoration to the proportion present before the operation, while after successful radical removal complete restoration to the previous standard was obtained, with sometimes positive gain. A woman who had gained thirty pounds after resection of a cancerous pylorus, showed after three months hæmoglobin to the amount of 65%. It would appear, therefore, as if some prognostic significance might be attached to an accurate estimation of hæmoglobin at intervals after removal of malignant tumors.

Everywhere, and until recently by all, the animal organism has been supposed to be one which could not live without air. It may well be one of the proud boasts of this present generation that it has shown that life of a complex organism is made up of the life of its component parts, mainly animal cells, and that, as Gautier has shown, at least one-fifth of it is *anærobic*. In other words, not all vital force comes from combustion, nor from the *ærobic* life of cells. But whether they need or eschew oxygen, the cells excrete products which must be expelled from the organization, else would the animal quickly succumb, were the carbonic dioxide, the urea, the water, or even the heat, which it produces, allowed to accumulate within itself. The products of ærobic life are poisonous and inimical enough, but those of its anærobic vitality are peculiarly so. They are of the same character as those which result from all bacterial activity, toxic, and for the most part, alkaloidal. Those of this class, constantly present in prolonged or violent putrefactive changes, belong to the pyridic and hydropyridic series, differing little from the bases of hemlock and tobacco; and even more powerfully poisonous substances are met with under similar conditions, such as muscarine. Since, then, we live anærobically, in part, we may expect to find such analogous substances as may result from the splitting up of albumenoid bodies, and these are the leucomaines. Let me here quote Gautier verbatim:

"The products of life, ærobic and anærobic, can not be retained within the organism for any length of time with impunity; normally, they undergo destruction and excretion by economic processes which are constantly in operation. But if from any cause the functional play is interrupted, should there be emotional disturbance of the nervous centres; should sudden chills suppress the action of the skin, or insufficient æration take place; or, if, finally, from any less obvious cause, leucomaine products be more abundantly formed within the cells, or be so defectively absorbed, excreted or oxidized as that the blood becomes charged with them, they are carried to the nervous centres, which regulate the central life and function as a whole; immediately disorder becomes general, complete, and necessarily assumes progressive forms—in a word, disease declares itself and undergoes development."—(Preface to Brown's "Animal Alkaloids.")

Like our proper cells ferments or specific microbes live—some of them—anærobically, as those of tetanus, malignant œdema, and some forms of septicæmia; while others live ærobically, like those of anthrax, pneumonia, etc. Others yet possess facultative powers in both directions, like tubercle bacilli. But each and every one *must* excrete, and ptomaines and leucomaines, like carbonic dioxide and urea, are the residual products of life, solid, liquid or gaseous, effete and pernicious, which may become the cause of disease, or may accompany it and mask the prime cause; and such they are, whether arising from the normal cells of the organism from within, or in the microbic cell introduced from without. Once set free within the system our tissues make no fine distinctions of origin or intended destination, but suffer in proportion to dosage of poison and susceptibility thereto.

We shall have to recur to this subject when dealing with the matter of surgical sepsis, so can afford to dismiss this aspect of it here, delaying only for the sake of definition and classification.

To follow all the chemical changes which the complex tissue molecule may undergo would be too foreign to our intent this evening. Yet it is not enough to merely say that a ptomaine is the alkaloidal waste product of a cell; it is in reality much more than this, since it represents the final production of a series of cyclical changes which represent tremendous cellular activity. Brown sums up the idea tersely when he says:

"A ptomaine thus presents itself as the residual skeleton, as it were, of the proteid molecule, which has undergone continuous disintegrative action, the ultimate terms of which are represented by the pyridic bases; so that, considered from a purely chemical point of view, a ptomaine may be defined as the cyclical nucleus of a proteid molecule, that has undergone complete destruction in the process of putrefaction."

The essential idea conveyed in the term is, then, that of *putrefactive* change, *i. e.*, one begun by cells introduced from without, and having no place in the healthy body, when everything is working smoothly.

On the other hand, it has been amply shown, not alone by Gautier, that the important chemical function of all animal tissue is the incessant elaboration of alkaloidal products formed at the expense of proteid material, just as carbonic dioxide and urea are simultaneously formed. Upon these vital and essential alkaloids, Gautier conferred the name leucomaines, which term he limits to those derived from albuminoid substance and formed in the living organism and before its death. It does not necessarily follow from this that the same base may not appear at one time as ptomaine, at another as a leucomaine, though this must occur comparatively seldom.

It will prove germane to our subject if we pause here to give a list of these alkaloids and bases, as well as to speak of a few other substances which, for lack of a better category in which to place them, we may call toxines.

Schwalbe, following a convenient and recognized system, has classified ptomaines and leucomaines as follows (*Deutsche Med. Woch.*, 1890, No. 36):

A. Ptomaines free from oxygen, whose bacteria are not yet known.—These persist throughout putrefactive activity.

Collidin ($C^8H^{11}N$). Isolated by Nencki, and regarded by him as isophenylethylamin. Appears to be formed only by a mixture of gelatin and hog's pancreas.

Pawolin ($C^9H^{13}N$). Separated from putrefying mackarel by Gautier and Etard.

Hydrocollidin ($C^8H^{13}N$). From the same; 7 mgr. kill a bird, with tetanic cramps.

Dihydrocollidin. Discovered by Cahours and Etard; made by treating nicotin with selenium

Neuridin ($C^5H^{14}N^2$). Found by Brieger in numerous rotting substances. Appears in putrefying human flesh in 3 days, increases to the 15th day, and then disappears. When absolutely pure is not toxic.

Cadaverin ($C^5H^{16}N^2$). Appears after 3 days in putrefying human flesh. Bocklisch found it in herring-brine, and in cultures of the Finkler-Prior bacillus. Dissolved in methyl alcohol it forms with iodide of methyl dimethylcadaverin. Is not toxic (according to Behring) in large doses. Causes inflammation and coagulation-necrosis (Scheurlen, Grawitz).

Putrescin ($C^4H^{12}N^2$). Found by Brieger in cadavers after the 4th day; also by Bocklisch in herring-brine. Effects like those of cadaverin.

Saprin. Discovered by Brieger. Quite similar to cadaverin. Not toxic.

Mydalein. According to Brieger this appears in cadavers after the 7th day. Is quite toxic. A few milligrams injected beneath the skin of a rabbit produce copious secretions from the nose, mouth, lachrymal and intestinal glands, as well as dilatation of pupils and vessels, and rise of temperature, with final somnolence; 5 mgr. kill a cat.

Several other more or less toxic alkaloids, to which names have not yet been given by their discoverer, Brieger. One of these causes violent diarrhœa and peristaltic motion.

B. Ptomaines containing oxygen, whose bacteria are unknown, are connecting links between ptomaines and leucomaines met with alike in dead and living tissue.

Neurin ($C^5H^{12}N)(OH)$. Previously known in nerve tissue, but found also by Brieger in cadavers. Is very toxic; 4 mgr. kill a rabbit, causing severe peristalsis, profuse sweating, contraction of pupil and of spleen, and tetanic cramp. Is antagonized by atropin.

Cholin ($C^5H^{15}NO^2$). Extracted by Stricker from bile. Is really both a leucomaine and a ptomaine. Is toxic in the same way as neurin, but much less so

Muscarin ($C^5H^{13}NO^2$). First discovered in mushrooms by Schmiedeberg; later found by Brieger in putrefying dorse or torsk (fish). Has been synthetically produced by oxydizing cholin with nitric acid. Is antidoted by atropin.

Gadinin ($C^7H^{16}NO^2$). Also extracted by Brieger from rotting torsk.

Two unnamed ptomaines, isolated by Pouchet, from the sewerage of manufactories where animal tissues are utilized.

Mydatoxin. Found by Brieger in putrefying human intestines and horseflesh. Slightly toxic.

Mydin. Same as above. Has marked reducing powers. Not toxic.

Methylguanadin. From rotting horseflesh. Is toxic and produces tetanic spasms.

Another unnamed ptomaine, found by Brieger in the same material, has powers similar to those of curare.

Mytilotoxin ($C^6H^{15}NO^2$). Isolated from the flesh of the limpet. Along with it Brieger found betain or oxycholin, which is not toxic; also a base which has marked sialogogue properties.

Peptotoxin. Discovered by Brieger in peptone, and found to have curarizing properties.

C. *Ptomaines isolated only from pure cultures of known species of bacteria.*—For these we are mainly indebted to Brieger, who also cultivated most of the organisms in media made with human flesh, in order to imitate our body chemistry as nearly as possible.

Typhotoxin. From cultures of typhoid bacilli.

Tetanin. From cultures of tetanus bacilli. Very toxic; producing first lethargy and apathy, then tonic and clonic spasms and death. Lately it is claimed that this has been extracted from the muscles of a patient with tetanus.

Tetanotoxin. Distilled from alkaline cultures of the above. Is weaker than tetanin, nevertheless strongly toxic.

Spasmotoxin. From same source, with similar properties.

A fourth toxic substance from this source produces also spasms, but especially causes copious secretion of tears and saliva. None of these four appear in the urine.

From cultures of the cholera spirillum *six* bases have been isolated—methylguanadin (*supra*), cholin, cadaverin, putrescin and two unnamed alkaloids.

To these I would add another class of

D. *Ptomaines produced by certain species of bacteria, though as yet not necessarily identified solely with such species.*

Tyrotoxicon, if produced exclusively outside the living organism.

Ammonia.

Trimelhylamine $(CH_3)_3N$). Both produced by staphylococci growing on beef or veal; the latter produced especially by the s. albus, by micrococcus prodigiosus and by streptococcus pyogenes. Both these are irritating, the former particularly in its nascent state. The latter if not strictly a ptomaine is a descendant of one or closely allied to one, and at all events is injurious in the same way.

TOXALBUMENS.

Save that they are not, strictly speaking, ptomaines, these bodies are produced in the same way (by bacterial action) and produce disturbance in analogous manner.

A toxalbumen has been isolated by Brieger and Fraenkel (*Berl. klin. Woch.*, 1890, Nos. 11 and 12) from cultures of Lœffler's diphtheria bacillus, which is an amorphous white powder, possessing fatal activities in small doses.

Other toxalbumens have been found by the same workers in cultures of the microbes of cholera, tetanus, typhoid, anthrax and of suppuration.

Leucomaines are alkaloidal substances produced during the life of the individual within his organs and tissues, by which they are entitled to rank as a class alongside of ptomaines. Their existence was first predicated by Gautier on purely theoretic or inductive grounds, which he then demonstrated to be correct by the discovery of a number of these substances. Roussy and Hugouneng first grouped them, about, as follows :

A. Betain-leucomaines.

Betain or oxyneurin ($C^5H^{11}NO^2$). First found by Scheibler in the red-beet. Liebreich found it in human urine and produced it synthetically by his different processes. Brieger found it in limpet's flesh. It appears to be identical with trimethyl glycocoll. Is not toxic.

B. Leucomaines of the uric-acid group.

Carnin ($C^7H^8N^4O^3$). Found in meat extract and brewer's yeast water.

Adenin ($C_5H_5N_3$). Met with in pancreas and spleen. With potassium hydrate forms water and "cyankali."

Guanin ($C^5H^5N^5O$). Common in both animal and vegetable world. Kerner found that the excretion of urea was proportional to the amount of it which he administered to rabbits.

Sarcin ($C^5H^4N^4O$). Found in living flesh. Isomeric and nearly identical with crystalline white powder.

Hypoxanthin.

Xanthin ($C_5H_4N_4O_2$). First found by Marcet in vesical calculi; then recognized in many organs.

Pseudoxanthin ($C^4H^5N^5O$). From muscles of swine.

C. Creatinin-leucomaines.

Creatinin $C^4H^7N^3O$). First produced by Liebig by treating creatin with hydrochloric acid; then recognized in urine. Has caustic properties. Ranke states that when introduced into the circulation it increases the irritability of peripheral nerves and produces muscle contractions.

Xantho creatinin ($C^5H^{10}N^4O$). Produces in small doses apathy, somnolence and nausea.

Cruso creatinin ($C^5H^8N^4O$). Resembles creatinin.

Amphi creatinin ($C^9H^{19}N^7O^4$). Same.

Two others isolated by Gautier, but not yet sufficiently studied.

D. Leucomaines of special secretions.

Viperin.	Poisonous secretions of reptiles and serpents. Their poisonous activities seem to be mitigated by the addition of potassium hydrate or sodium carbonate.
Echidnin.	
Salamandrin.	
Cobraïn.	
Crotalin.	
Najin.	
Elaphin.	
Cedrin.	
Valdivin.	

According to Calmels the primarily active agent in all of these albuminoid secretions is *methylcarbylamin*, which he believes to be produced in the cells of the gland in a nascent condition by the action of formic acid upon glycocoll. This methylcarbylamin seems to have frightfully poisonous properties, inhalations of it killing rabbits in a few seconds. Schwalbe also states that equally poisonous substances are secreted by certain fish in Chinese and Australian waters.

Protamin. Discovered by Miescher in semen.

Spermin. From same source.

E. Leucomaines from particular organs.

The eyes contain *neurin*, the brain *neurin* and *cholin*, the heart, lungs and blood the former. In fresh veal Guareschi and Mosso *methylhydantoin.* Wartz examined expired air and there found two bases, *ammonia* and another gaseous alkaloid not yet named. Brown-Sequard and Arsonval have also discovered a gaseous base in expired air, which produces in rabbits a lowering of respiration rate and an exaltation of pulse, contraction of the pupil, and fatal diarrhœa with colic. From the fresh spleens of swine Morelle extracted two bases, one of which kills frogs in five hours after complete paralysis of sensation. In urine a new base has been discovered by Pouchet. Bouchard has shown how those diseases which accompany or are caused by increase of putrefaction in the alimentary canal are characterized also by a greater excretion of leucomaines with the urine.

F. Leucomaines which are produced in the bodies of patients and of diseased animals

Pyocyanin belongs in more than one of these sections. Has been isolated from pure cultures of bacillus pyocyaneus, as well as from pus, blue sweat, etc. In contact with oxygen it changes to *pyoxanthose.*

Cadaverin and *putrescin* have been found in the urine and fæces of patients suffering from cystinuria; consequently we must probably consider cystinuria as due to intestinal mycosis.

Spermin, discovered by Schreiner in human semen, has been found in cultures of the cholera spirillum.

Phlogosin was separated by Leber from cultures of staphylococcus aureus. It causes inflammation when injected.

Dimethylamin has been found in sausage and in fish.

Triethylamin, *prophylamin*, *tyrotoxicon*, *etc.*, also deserve mention here, though it may be hard to assign them their exact positions in such a classification.[1]

As a positive demonstration of the formation of ptomaines by bacterial action there are perhaps no experiments more illustrative and convincing than those of Poehl. It is known that most at least of these alkaloids give color reactions with various salts, especially with those of iron.

Poehl mixed very small proportions (0.05%) of perchloride of iron and ferro-cyanide of potassium with his nutrient media, and then cultivated various organisms thereon. In some cases slowly, in some rapidly, the color reaction appeared along the needle streak. Inasmuch as the resulting Berlin-blue, due to the reducing power possessed by the microbes, only forms in a slightly acid medium, the acid had sometimes to be added to previously alkaline or neutral gelatine jelly in which alone certain bacteria will grow. On the addition of nitric acid to cultures of cholera spirilla there developed beside the Berlin blue a reddish hue, which is also the case when these organisms grow on jelly free from either of these salts; this is probably identical with the skatol derivative found by Brieger in the urine of certain patients.

Poehl, by the way, observes that the Finkler-Prior bacillus needs a smaller proportion of acid to produce a similar reaction than Koch's spirillum, and recommends on these grounds the administration of oxidizing substances, like peroxide of hydrogen or permanganic acid, in order to check the formation of ptomaines and decompose those already formed.—*Lancet*, October 30, 1886, p. 830.

But I must hasten along to consider the more exclusively surgical topics to which I desire to invite your attention throughout the remainder of this evening, and for the balance of this series of lectures. It is mainly to the matter of the surgical infectious diseases that this course is devoted, in other words to the mutual reactions of animal and vegetable cells.

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[1] For further informaton the reader is advised to consult the excellent little monographs of Vaughan and A. M. Brown.

Neelsen has divided the infectious diseases generally according to their bacteriological peculiarities, as follows:

1. General acute mycoses of the blood. (Anthrax, septicæmia of mice, etc.)
    a. Toxic (Septicæmia.)
    b. Intermittent. (Relapsing fever.)
2. Localized bacterial infections.
    a. Local, with secondary general poisoning. (Putrid fever, cholera, tetanus.)
    b. Local, with the general characteristics of inflammation, (Pneumonia, malignant œdema.)
    c. Local with necrobiotic tendencies. (Hospital gangrene, progressive necrosis.)
    d. Local, with pyogenic tendencies. (Suppuration.)
3. Mycoses of the blood with secondary local lesions. Measles, rötheln, scarlatina, variola, diphtheria, osteomyelitis, acute rheumatism, chicken-pox, cholera.
4. Mycoses with tissue proliferation; or the infectious granulomata.

This classification is logical providing it be quite correct, but it is questionable whether the diseases included in his third and fourth classes are in effect *mycoses*, and whether they are not due to some other parasitic form of life than the mycotic. Be this as it may those troubles which concern us at present are undoubtedly mycotic in origin, and we need only discuss some of their general phases before proceeding to special forms. And first of all and among the most important are:

CONDITIONS PREDISPOSING TO INFECTION.—These conditions must be studied on the part of the body infected and on the part of the organism which produces the infection. First of these it must be laid down as a general rule that the normal healthy tissues of the human body neither harbor infectious organisms nor favor their development when introduced. In other words, the highest type of tissue vitality presupposes a condition which is inimical to the action of any pathogenic bacterium. Furthermore, that such organisms, when introduced by accident into the circulating fluids of such a typically healthy body, are quickly destroyed in the circulation or in the tissues. Certain organisms disappear from the blood with remarkable rapidity, others are deposited in various tissues or organs where they are quickly disposed of, while yet others probably are excreted through some one of the various emunctories. When organisms disappear with such rapidity from the blood, it must be because they are quickly destroyed. Within the past year a number of papers have been published with reference to the antiseptic properties possessed by blood serum. It is well known that the blood serum of different animals varies very much in this capability as well as in its action with regard to different species. That the serum of rats' blood possesses a high degree of resistance in this direction has long been demonstrated by numerous laboratory experiments. Indeed so resistant is the common rat to most of the bacteria which are pathogenic for the human species, that extensive wounds can be inflicted upon them and not only no dressing be applied, but every opportunity for septic infection afforded, and still without the slightest apparent effect. Numerous experimenters have injected into the venous circulation various species of known organisms, and then have made or attempted to make cultivations from the blood at intervals varying from a few hours to a few days. It has been found that the rapidity with which they disappeared from the blood varied with the species employed, and according as it was or was not spore-bearing.

According to Wyssokowitsch, when small quantities of spirillum tyrogenum, a non-pathogenic and non-spore-bearing bacterium, were injected in the blood stream they were found in greatly diminished numbers after five minutes, and had completely disappeared in seven. In other cases spores were rapidly deposited from the blood but retained their vitality for several days. In the case of bacillus subtilis, a few were found alive even after seventy-eight hours. Apparently they were deposited in the endothelial cells of the smaller vessels and chiefly in the spleen. The streptococci pyogenes, which do not exert a pathogenic action when introduced into the blood of rabbits in small numbers, were much reduced in number after seven hours, and disappeared after fifty.

From Wyssokowitsch's researches it would appear that organisms which do not rapidly die are deposited like particles of pigment; thus anthrax bacilli, introduced in moderately small quantities into rabbits, were found to have disappeared from the blood after twenty-four hours, though they were present in large numbers in the spleen and liver. That organisms may be excreted by the kidneys is shown by various observations, and, as Cheyne points out, it affords a very plausible explanation for certain cases of pyelitis and bacteruria occurring in patients who have never had any instrument passed, and whose ureters and bladders are perfectly normal. The explanation being that these organisms had entered the blood in a living state, had been excreted by the kidneys, and had afterwards found a suitable culture medium in the urine and grew in the pelvis of the kidney, or in the bladder. Thus Ogston states that he has found micrococci in the urine of patients suffering from septicæmia, though these patients apparently had no disease of the urinary organs. This statement seems quite positive, although some have denied the excretion of bacteria by the kidneys, and claim that they only appear in the urine after rupture of blood vessels. So, too, in pyæmia and some other diseases, for example in Ribbert's experiment with aspergillus. There is a marked tendency for the organisms to locate in the kidney, which would seem to indicate some functional or anatomical attraction by which they are drawn thither. Ribbert in his investigations concerning the cocci of osteomyelitis in the blood, found that after twenty-four hours they could be demonstrated in all the organs by Gram's method, but that later they disappeared from all except the kidney. Experiments elsewhere alluded to in these remarks demonstrate their excretion by the mammary glands, and are of interest in that they show that the organisms which cause abscesses of these glands may be deposited there from the blood, although undoubtedly the majority of abscesses of the breast are caused by the inward spread of bacteria from the surface. The frequent occurrence of abscesses, especially metastatic, in the parotid gland, after suppuration in other parts of the body, finds here also, perhaps, its most easy explanation. Passet has even stated that cocci were excreted through the conjunctiva in the case of mice and his statement is confirmed by Longard.

Embolism, as a factor in provoking suppuration.—Attention has already been called to the large part played by emboli in surgical inflammations and affections, since there is no limit inside the living body to which infected emboli cannot be transported. Ribbert, while studying the death of fungi in the body, met some beautiful demonstrations in this direction. On comparing his experiments with aspergilli with those made with mucor, he found that in the former case deposits were formed in various organs and muscles, while the spores of the latter gave rise to deposits in organs only, the muscles being not affected. Referring this discrepancy to the relative size of the spores, the mucor spores being much smaller and passing more easily through the capillaries, he endeavored to increase their size before their introduction into the blood, and so kept them for a short time in a nutrient fluid. In consequence, they swelled up and commenced to sprout, and then he injected them into the circulation, when he found no difference between his results. The inference to be drawn from these experiments is very obvious, showing that organisms will or will not obstruct the capillaries in proportion to their size. Working in the same direction Ribbert found that the staphylococci would pass through the circulation, to be arrested in the kidneys, but that if pyogenic cocci were attached to larger particles which could not pass the capillaries, he could only produce myocarditis and endocarditis. For this purpose he cultivated the microbes on potatoes, and in removing them for experiments secured a mixture of potato granules and bacteria. If the particles of potato were very fine, only myocarditis resulted; if they were grosser, endocarditis appeared as well. Bonome studied nine cases of gangrene of the lung in man, and discovered staphylococci in all of them. Injecting cultures of these organisms into the blood of rabbits, he failed to cause any gangrene there, but by mixing them with very fine pieces of elder pith, and then injecting this mixture in the jugular vein, he produced numerous embolic lesions in the lungs, which led to coagulation necrosis and extensive gangrene, while injections of fragments of pith alone produced no effect. So also, Pawlowsky found that simultaneous injection of sterilized cinnabar and of cultivations of staphylococcus aureus produced abscesses in various organs and in fact typical pyæmia.

General depression of vitality.—This has been recognized as a cause predisposing to suppuration for centuries, long before its active causes were thought of. Thus by administering large doses of phosphorus for some time to animals, such changes are produced.

Thus too such conditions as those brought about by starvation, by overwork, by vitiated food, by exposure, possibly even by mental worry, will so far reduce the vulnerability of previously healthy tissues that they succumb much more readily to bacterial infection. Such experiments as those made by Arloing, Cornevin and Thomas, are more than suggestive. They, inoculated some frogs with rauschbrand, and placed them with others not inoculated in vessels containing water at 22 C. After fifteen to thirty hours the inoculated frogs died, and in their lymph-sacs the rauschbrand bacilli were still active and virulent, while the uninoculated frogs remained well. In contrast with this, other frogs inoculated with the same germs, but kept in cold water, were unaffected.

The experiments of Charrin and Roger (*Arch. de Physiol.*) show that great fatigue favors infection. Animals that have been violently exercised died in shorter time, after inoculation with symptomatic anthrax, than those that had not been fatigued.

Local depression of vitality.—This is a cause more easily recognized, at least, if not more generally met with. When a given part has been deprived for a time of its natural blood supply, bacteria grow in that part much more readily than if such supply had not been interfered with. Thus, according to Cornil, a septic nephritis is readily obtained by ligating the renal arteries for some hours, then removing the ligature and injecting pyogenic organisms in the blood. The experiments made by Chauveau, termed the *bistournage*, point unmistakably in the same direction. Heubner's experiments in artificially producing diphtheria are most demonstrative. He ligated the vesical arteries for two hours, by which he produced intense congestion and submucous œdema of the fundus of the bladder, in consequence of which the epithelial cells died. After removing the ligature and thus restoring the circulation, there was copious exudate with coagulation necrosis. He found that if at the same time that he restored the circulation septic bacteria were injected into the blood, they accumulated in large number at the seat of these changes, it being only necessary that comparatively large numbers should be introduced. It is also stated by Cornil that if a slight nephritis is set up, either by cantharides or in some other way, and if then pyogenic organisms are injected into the blood, a septic peritonitis occurs.

Inflammation.—Obviously this is the most conspicuous illustration of local depression of vitality, and has long been recognized as preceding most every suppuration. Cheyne divides inflammation into three stages, the first including all the phenomena up to and including exudation; the second the substitution of granulation tissue for that originally attacked, and the third comprising the cessation of irritation and the changes which lead to the formation of a scar. During the first stage the natural vital activity of the part is suspended, and it is usually during this stage that organisms enter. It has been found that pyogenic cocci are not as likely to settle and infect a part which is acutely inflamed as in one where inflammation is less severe, where, apparently, they most usually pass out of the blood vessels. Thus Rinne, in experiments to be referred to later, found that a violent inflammatory action did not produce a point of least resistance, but that a slighter injury or disturbance, such as might be caused by the chemical products of bacteria, sufficiently weakened the part to enable the organisms to grow in it. Thus acute osteomyelitis and local tubercular disease much more often follow an injury of slighter severity, and very seldom occur after an extensive lesion. Fractures in consumptives are seldom if ever followed by local tuberculosis, while slight sprain is frequently assigned as the cause of such a process.

Cold.—A brief or long exposure to cold is so often mentioned as a cause for existing inflammations that it ceases to have much weight with the careful observer. It is only by careful experiment upon animals that its etiological importance can be determined. Lassar shaved a number of rabbits, and so long as he kept them at a suitable temperature they remained in good health. If plunged into ice cold water for from one to three minutes, and then carefully dried and warmed again, they almost always developed albuminuria with hyaline casts and with elevation of temperature. These animals often recovered to suffer in the same way again when similarly exposed. Microscopic examination showed that they had developed an interstitial nephritis. As more directly bearing upon our subject, the experiments of Grawitz on the relation of peritonitis to cold must here be mentioned. He shaved the abdomens of young animals, covered them for a short time with warm compresses, and then allowed a draught of ice cold air to play on the parts for twenty to forty minutes, and yet without noticeable effect.

Injury.—Injury acts in two ways. First by producing the first stage of inflammation, secondly by causing effusion of blood, and permitting an escape of any pyogenic cocci which may be there circulating, at a point where they may find a quiet medium suitable for their development. Prudden's studies of endocarditis have well shown the effect of injury, which is in large measure due to loss of resisting power of the endothelial and connective tissue cells. Since every wound must be followed at least by a conservative amount of inflammation it can be seen how operation wounds should be really included among injuries. Experimental work with symptomatic anthrax, which is only produced by bacilli acting in the tissues and not in the blood, affords ample illustration. If the bacilli of this disease are injected into the blood, the animals remain well and the bacilli soon disappear. But if immediately after their injection, a bruise be inflicted on some part of the body, by the aid of which the bacilli may escape from the vessels, soon the characteristic tumors form and the disease rapidly progresses to a fatal termination. Cheyne published the case of a drunkard in poor health suffering from albuminuria, who developed an abscess whenever and wherever he received a bruise. And every practitioner meets with analogous cases; in such instances the pyogenic cocci are alive in the blood, and the combination of lowered vitality, toxæmia and injury bring about the suppurative result.

LECTURE II.

WOUND INFECTION AND SUPPURATION.

SYLLABUS.—*Predisposition to Infection, continued.*—Influence of manner of inoculation and arrangement of tissue; of irritating chemical substances. Miscellaneous influences. Variation in susceptibility. Concurrent growth of various bacterial species. Recognition of pyogenic cocci in the blood as an aid to diagnosis.

A Study of Pus.—What is pus? Different substances to which the name has been applied. Study of its gross and minute appearances, and circumstances under which it is produced. Virchow's views as to physiological and pathological irritations, and his four degrees of the inflammatory process. Old "humoral" theory. Cohnheim's teachings and their influence. Can we have pus without micro-organisms? Experiments with cadaverin. Study of the discharge from granulating wounds. Differences between acute and chronic abscesses, and the material they contain. Metastatic abscesses and *loci minoris resistentiae.* Minute anatomy of abscess.

The "pyogenic membrane" should be called "*pyophylactic*" membrane. Differentiation of so-called pus into true *pus*, *puruloid* and *archepyon.* Conclusions.

POINT OF INOCULATION AND ARRANGEMENT OF TISSUE.

BACILLI vary very much in their pathogenic effects, depending largely on the point where introduced, and the character of the tissue in which they are placed. Some organisms will not grow at large in the body, but only in certain tissues, while the character of the lesion may vary within wide limits, according to that of the tissue in which they thrive. The higher fungi act to best advantage within capillary blood vessels or large serous sacs. The bacillus of malignant œdema grows only in the cellular tissue, and the cocci of erysipelas thrive best in the lymphatic vessels and cellular tissue. Cheyne had some very suggestive results in experimenting with the *proteus vulgaris*, which is a common saprophytic organism. Introduced in quantity into subcutaneous tissue it provoked only abscesses, but the same amount introduced into the muscles would prove fatal, while a very small dose in the muscles was sufficient to produce abscess. He suggests that possibly some chemical substance in the muscle is split up and gives rise to poisonous compounds. Analogous results have been obtained with other bacteria. Fehleisen states that about one-twelfth of the quantity of staphylococci which is necessary to provoke peritonitis will cause suppuration in and around joints. He thinks also that pus varies in virulence according to its origin, different tissues probably producing different ptomaines. As affording the best illustration of the above statement Cheyne adduces the disease known as the *Black-leg* in England, *Rauschbrand* in Germany, or *Symptomatic anthrax* in France. It affects chiefly cattle and sheep, and is characterized by the rapid appearance of irregular nodules in the skin and muscular tissues, these being at first tense and very painful, but rapidly becoming painless and crepitating. It is accompanied by fever, usually high, but is generally fatal in from 36 to 40 hours. It is caused by anærobic bacilli, which are remarkable for the conditions by which they produce death. In order to affect the animal to this extent, they must be introduced either into the subcutaneous tissue or into the muscles. If injected into the veins or the bronchi they do not kill, but apparently die out after a little, leaving the animal protected against the disease. If after the virus has been injected into the veins a bruise is caused in some part of the body, the bacilli reach that spot and set up the disease. Inoculations made at the tip of the tail in cattle cause only a small amount of reaction. The nearer the body the more marked the disturbance. All of which is to be explained partly by the dense tissues of the tail, and partly by the low temperature of the part, since if after inoculation the tail be wrapped in bad conductors of heat the reaction can be very much increased, and *vice versa*.

So far as the pyogenic organisms are concerned, most of them act in the cellular tissue, to which they gain access commonly after removal of the epithelium. The gonococcus appears to be the only bacterium which can penetrate uninjured epithelium, and even this only attacks certain mucous membranes. Bumm has shown that pure gonorrhœal pus may be injected into the subcutaneous cellular tissue without causing reaction, which proves that pus, apart from the microorganism contained in it, is not itself pyogenic. Moreover in such a case, if an incision into the part be made twenty-four hours later, the pus cells will be found in good condition, while the cocci have disappeared, which would seem to indicate a phagocytosis in this instance at least. As seen elsewhere, the pus of gonorrhœal buboes contains, not the gonococcus, but the ordinary pyogenic organisms, showing that such buboes are the result of mixed infection, the same being true of periurethral abscesses.

We have also evidence that the arrangement of tissue influences pyogenic action in the frequency with which pyæmia follows acute osteomyelitis. This is apparently due in large part to the great pressure to which pus is subjected in the interior of bone, and this high pressure is proven by the manner in which fat oozes out of bone when it is trephined; also by the occurrence of fat embolism in the lungs. There are numerous other illustrations, if one needed to introduce them, which go to show that bacteria appear to exercise certain selective affinities which are to be explained, we must suppose, by certain peculiarities in the tissues selected. The same is true of the higher fungi, like the pathogenic forms of mucor and aspergillus, the latter in the rabbit selecting the membranous labyrinth; which selection, in this instance, affords us an explanation of the rotary motion so characteristic of this disease in rabbits.

Irritating Chemical Substances.—These, when concentrated, destroy the vitality of tissues, and when more dilute, set up at least the early stage of inflammation. The effect of such substances in producing a weak spot is no doubt the explanation of Kocher's result concerning acute osteomyelitis. He induced digestive disturbances by introducing large quantities of septic material into the intestinal canal. He then injured a bone by injecting ammonia or some other chemical substance into it, after which acute osteomyelitis occurred at the seat of injury, while the one disturbance without the other produced only temporary reaction. Experiments in the same direction, but slightly varied, give always the same result. The bearing of these investigations upon the development of blood poisoning in human beings can hardly be overestimated, and we shall have more to say about it when speaking of intestinal toxæmia. Cheyne argues from such facts as these that it is questionable whether, in granulating wounds which have become septic, it is well to wash them out with irritating antiseptics, as we so often do, unless these solutions are able to kill all the micro-organisms present in the wounds, and thus render them aseptic, fearing lest the chemicals might so far injure the granulation wall as to produce a weak spot in which pyogenic cocci might develop, and from which they might enter the circulation. Thus it has been found that in cases of tubercular abscesses of bones and joints disseminated tuberculosis occurs much more frequently where the sinuses have become septic, and more especially where these septic sinuses have been much irritated by inutile antiseptic injections. So he would avoid the use of carbolic acid, for instance, and simply wash away the discharge with some fluid which will not injure the granulation wall. Considering the known properties of peroxide of hydrogen, this may be an indication for its use in these cases. Of course, except in the case of wounds, the chemical substances, by aid of which bacteria gain a foothold, are themselves products of bacterial action. That many of these are wholly poisonous is now well known. Two of the ptomaines which have been most commonly experimented with are cadaverine and putrescine. These are products of putrefactive bacteria, rather than of the pyogenic. As we shall show later the pyoid material which has occasionally been found after the introduction of cadaverine is not entitled to the name of pus, when it is, as it has been stated to be, sterile, since, according to the view adopted in these lectures, there is no fresh pus which is free from organisms. So far as the pyogenic cocci are concerned, Brieger states that he has been unable, at least until recently, to obtain from cultivations of these organisms, any true toxine. When the staphylococcus aureus or albus is cultivated on moist beef or veal, ammonia is given off, and the latter produces in addition tri-methylamine, the streptococci likewise producing both of these substances.

Ammonia is naturally irritating. The latter is closely allied to the ptomaines, and when present in considerable quantity is noxious. When these bacteria are cultivated in milk they rapidly set up pure lactic fermentation. This fermentation undoubtedly takes place in wounds, causing acidity of discharge and watery or very thin pus. That fever in suppurative disease may be explained by increased tisssue change as the result of bacterial growth without the necessary production of ptomaines, may be argued by analogy, as Baumgarten states in the case of the fever which occurs in trichinosis, where there is no idea of the action of ptomaines.

(Leber, a couple of years ago, claimed to have recovered from cultivations of staphylococci a crystalline substance which he called phlogosine, and which he said produced pus when injected into animals. *Fortschritt d. Med.*, 1888, No. 12, But since his publication we have heard little or nothing of this substance.)

Certain other influences also exert a decided effect in favoring suppuration, many of which figure prominently in the condition of the blood. Furuncle, carbuncle and other suppurative affections are known to occur frequently in cases of diabetes. Very recently Bujwid (*Centblt. f. Bakter.*, Vol. 4, p. 577) has studied this matter experimentally. He first found that staphylococci do not grow well in media containing 5% of grape sugar. He then ascertained that a given number of these cocci, insufficient to cause an abscess when injected alone, will do so when injected along with the fluid containing 25% of grape sugar. Also that a given quantity along with

12% of grape sugar did no harm; but that if in another animal the same quantity was injected and then a 12% solution of grape sugar was injected daily at the same spot, an abscess formed. Variations of these experiments, and their confirmation by Karlinski, show that the presence of grape sugar in the tissues so depresses their vitality that the pyogenic cocci can act in much smaller numbers and more vigorously than would otherwise be the case.

Dilution of the blood also interferes to some extent with the rapidity with which bacteria are killed in it. If water in quantity be injected along with non-pathogenic bacteria, they do not disappear from the blood so quickly as when injected without it. For other causes which may be included under this caption we must refer to Cheyne's excellent monograph.

There are extraordinary variations between different animals in regard to susceptibility, which are extremely significant. For instance, in the case of mouse septicæmia, a mouse will die as a result of the injection of a single bacillus, while a rabbit will tolerate the injection of 4cc. of jelly cultivation, containing millions of bacilli, with only slight local symptoms of swelling and redness. So too with so-called chicken cholera. A single organism is enough to determine the death of a rabbit but two or three hundred thousand are necessary to kill a Guinea pig; while ten thousand may produce an abscess, and less than that number have no perceptible effect. Cheyne has deduced from such results as these certain laws which he formulates as follows:

1. The pathogenic dose of a virus varies inversely with the predisposition of the animal to the disease in question.

2. In animals which are not very susceptible to a disease, the severity of the infection varies directly, within certain limits, with the amount of virus introduced.

Some as yet unexplained phenomena must be grouped under the heading of increased virulence,—a phenomenon well-known to all but quite inexplicable. For instance with regard to the bacilli of symptomatic anthrax, it has been found that the addition of a minute quantity of lactic acid to cultures increases the virulence of very attenuated virus in a short time, even one-fifth of one per cent will double their virulence in twenty-four hours. So the pyogenic cocci when grown in milk produce lactic acid, although there is no evidence that their virulence is thereby increased. Ogston discovered that if he grew pyogenic cocci in eggs, their activities were notably augmented. On the other hand, lactic acid does not increase the activity of the pneumococcus which loses its virulence most quickly when grown in milk. Such facts may not yet have a practical bearing for us, yet they show by what slight and unexpected causes virulence may be altered. Experimenters are well aware of the changes produced by passing organisms through animals. For instance, Pasteur discovered that the bacilli of swine erysipelas are weakened by passing through pigeons, while the bacilli of rauschbrand are strengthened by passing through very young guinea pigs from one to three days old. The results of passing anthrax through animals, as well as of the unknown contagium vivum of hydrophobia, are well known. Also that in order to keep cultures of bacillus tuberculosis active they must be passed through animals every three or four generations.

Anthrax bacilli, in minutest doses, in mice, guinea pigs, etc., produce a rapid general, septic, fatal infection; in dogs and in older or larger animals very small doses have little or no effect, and larger ones cause carbuncle or œdema. In man they cause usually only malignant pustule, which has seldom any marked septic effect. The pnemonococcus when injected into the tissues of mice and rabbits produces a rapidly fatal septicæmia; only when injected into their lungs does it cause pneumonia.

So with the pyogenic cocci. Often after their injection in dogs no result follows. In man the item of individual susceptibility is one of great importance and at the same time of great variability. The immunity from septic complications which the wounded Turks displayed during the Turko-Russian war was remarked upon by German military surgeons. Undoubtedly they were not lacking in opportunities for developing sepsis, yet they displayed such vital habits as made their bodies unfavorable soil for bacterial development.

Or to put this same idea in the words of Prof. Welch (in a private communication): "The pyogenic cocci are a curious group of organisms which it is difficult to bring into line, as regards their pathogenic properties, with other infectious bacteria. Their effects seem to vary strikingly with their degree of virulence, with the number inoculated, with the place and manner of inoculation, and with those mysterious conditions which we call predisposition but which we little understand. And then, what a variety of pathological conditions they are capable of producing—from an innocent pustule to the most malignant pyæmia or ulcerative endocarditis."

It is of no small importance to consider the effect of the simultaneous growth of two or more species, by which pathogenic power may be at one time increased, at another diminished. In man, in all probability, pyogenic activity is thereby increased as is shown by the frequency of mixed infections. For instance, in wounds to which numerous species have had access a struggle probably results that terminates in favor of the pyogenic cocci, and this may be further complicated by the activity of saprophytic forms. Thus the foul smell of a wound, if present at all, usually subsides as time goes on, especially if drainage be good, showing that putrefactive bacteria gradually cease their activity. Nevertheless the ptomaines produced by the latter, when taken into the system, depress the vitality of the patient, and thus better fit these tissues to support the pyogenic cocci; while locally such products are injurious, as elsewhere described, owing to granulation tissues about the wound, and thus may open the way for systematic pyogenic infection. So Cheyne states that if a sinus leading to carious bone, whose wall is lined with membrane containing tubercle ('pyophylactic'), becomes infected by these cocci the result is a more rapid growth of the tubercle bacilli, by whose development general infection is made more probable, *i. e.*, local depression of vitality enables the tubercle bacilli to grow more luxuriantly. We shall have more to say on this subject when dealing with the subject of mixed infection.

The concurrent growth of bacteria is perhaps in no place better illustrated than in the pus coming from a wound which has produced tetanus. When speaking of this disease we shall call attention to the method by which the bacilli of tetanus may be isolated from other forms; but so far as their co-existence is concerned we have a significant demonstration of the simultaneous growth of aerobic and non-aerobic organisms; the former consuming the limited amount of oxygen present, and really producing the conditions necessary for the best growth of the bacillus of this dread disease.

Perhaps one finds no more conspicuous illustration of the various degrees of immunity enjoyed by different animals than can be met with in the susceptibility of different species to anthrax. A single bacillus introduced into a guinea pig certainly proves fatal, while rats often survive inoculation, apparently suffering little or not at all, this depending largely upon the age of the animal. The older the rat the fewer general symptoms does it manifest; the thicker the pus met with at the seat of the injection, the more rapidly do the anthrax bacilli perish.

There are other times when it is to the advantage of the patient to be the host of more than one species of pathogenic organism, thus taking advantage of certain antagonisms—some of which are well known. Ememerich has shown the value of the cocci of erysipelas, in rabbits, as protective against anthrax and even curative. His experiments have been confirmed by Mattei and by Pawlowsky, and the latter found no small degree of antagonism between anthrax bacilli on the one side and the micrococcus prodigiosus and the pneumococcus on the other. Whether the explanation be that the cocci by themselves prevent the growth of the bacilli, or that they irritate the phagocytes and increase their destructive power, or whether there is produced some chemical substance which is poisonous to the bacilli, is not known. It suggests, at all events, a possible treatment for anthrax in man by inoculation with erysipelas, and it at least raises the question whether, if tumors are really of parasitic origin, the well-known fact that they sometimes disappear after a local erysipelas, or after an erysipelas deliberately produced by inoculation, may not enjoy the same explanation. It will be seen further that the treatment for phthisis, by inhalation of non-pathogenic organisms, as already tried, may, after all, have a rational basis, although so far unsuccessful.

Duclaux, in his work on "Microbes and Disease" gives an excellent example of the part played by other factors in relation to infection. The itch of domestic animals is produced by an acarus which may be almost seen with the naked eye, and which lives in the superficial layers of the skin. According to the experiments of Delafond and Bourgingnon, this insect when placed on the skin of well nourished healthy animals does not penetrate nor propagate. Healthy sheep cannot be artificially inoculated with itch, but if they are first submitted to unhealthy surroundings as regards nourishment and stabling, then the acarus can be very readily implanted, and will flourish so long as the animals are thus kept. Just so soon as their nutrition is improved and their stalls cleaned and aired, then without treatment against the acarus the itch disappears, and the animal becomes clean. The same differences notably affect the silk-worm in France. The disease known as *pebrine* attacks silk-worms, irrespective of their state of health, while *flachérie* attacks worms only whose digestive apparatus is weakened by disease or heredity.

The recognition of pathogenic cocci in the blood, as an aid to diagnosis.—The statement has been already made, and is confirmed by so many observers, that the normal blood of healthy animals does not tolerate the presence of pathogenic organisms nor harbor them, that it scarcely needs repetition here. Nevertheless, it is well-known that two propositions, each the converse of the other, may be accepted as true; first, that, in a condition of lowered vitality, they may be present in the blood, and second, that when met with in the blood, they are significant portents of impending evil. Although this has been in a general way recognized for some time, Eiselsberg has been perhaps the first to make practical application of the fact and to introduce to the profession a new diagnostic aid of some practical utility.

In the *Wiener klin. Woch.*, September 18, 1890, he has reported four cases of supervention of high fever after injury or operation, where the diagnosis of impending or present septicæmia was made by a bacteriological examination of the blood, and confirmed by subsequent events. That such an aid to diagnosis is not usually called for, will be generally allowed, yet that it may have no small value is illustrated by one of his cases, where for some days diagnosis wavered as between an actual rheumatic affection, and osteomyelitis—in which the discovery of pathogenic cocci in the blood and their successful cultivation both cleared up the case, and furnished an important indication for operation. In three of these cases staphylococci were found, in the other streptococci. Aside from these instances in which the examination had a diagnostic value, he reports several other undoubtedly septic cases;—for instance, three progressive phlegmons, one acute osteomyelitis and four cases of septic peritonitis, which were carefully examined, and in three of them staphylococci were found. He alludes also to the rapidity with which these organisms develop in the blood after death, and reports a most interesting series of *post-mortem* observations in which cultures were made from the blood of an individual dying of sepsis, at intervals of 10 minutes, during the two hours immediately succeeding death, from which it appeared that they developed at an almost arithmetical ratio.

Having now discussed at some length the causes which predispose to infection we are better prepared for an attack upon the obscure, and yet tremendously important topic, of suppuration or the formation of pus and a rehearsal of some of its properties and varieties.

Suppuration and Pus.

What is pus? A few years ago this question was comparatively easily answered. That it is now a query to which it is extremely difficult to give an explicit answer, is simply an evidence of progress in the study of pathology. A former and revered teacher used to express it tersely that "pus is dead or dying blastema." Even the term blastema is now almost obsolete. According to Robin, blastema means "the substance resulting from the elaboration of nutritive material furnished to the anatomical elements by the blood." Foster's dictionary gives as other definitions: "Undifferentiated embryonic tissue; the material out of which a part is to be formed;" and, "a free or parenchymatous plastic exudate." These definitions are sufficiently succinct to indicate that dead or dying blastema must be good and valuable material going or gone to the bad. In a rough and off-hand way, therefore, this conception of the term pus may be considered sufficient as a working basis for a further study of the substance itself.

But, as generally used by the clinician, the term is applied alike to the contents of acute or cold abscesses, which have never known exposure to the air, to the discharge from mucous, as well as granulating surfaces, and to the fluid or semi-solid results of degeneration of various tissues. Are these various substances identical, and do they deserve the same name? This is a vexed subject in the domain of surgical pathology, to a discussion of which the balance of this lecture is in the main devoted.

Many and many a time have I seen my operation wounds heal by primary union, under an aseptic dressing. Of them I could say, as we usually do under such circumstances, they healed without suppuration. And yet, if the drainage tube—supposing one had been used—had been left *in situ* a few hours too long, there would be found about its opening, or in its lumen, a drop, perhaps a few drops, of creamy, semi-solid material, which we should ordinarily call pus. Is this material identical with the pus from an acute abscess? To this inquiry I have devoted no small time and study, both at the desk and in the laboratory, and such conclusions as I have reached shall appear further on.

There is a popular expression: "There are dogs and dogs." Must we not say also, "There is pus and pus."

This subject can only be approached by a careful study of the gross and minute appearances of pus, and the circumstances under which it is produced. A study by which these questions may be answered is inseparable from a study of inflammatory phenomena, with which I must then, for a little while again detain you.

Virchow has made this distinction between physiological and pathological irritation (Reiz), that in the former case the function of the cell, or the collection of cells (the organ), is simply increased; in the latter it is disturbed. The entire process by which an alteration or disturbance of nutrition is thus brought about by irritation he considers to be a progressive process, but not necessarily an inflammation. It might result in hyperplasia (numerical cell-increase), inflammation, or tumor formation. He classified irritations as mechanical, chemical and physical, *i. e.*, thermic and electrical. Only such irritations as lead to inflammation interest us here, and, as we shall see, in considering pus formation that we shall have to practically limit ourselves to a consideration of micro-organisms as the sole causes of such irritation.

At that time (1870) Virchow distinguished four degrees of the inflammatory process:

1. A form distinguished—aside from changes in the cells themselves—by watery, serous, albuminous, or mucinous exudate.
2. A form in which the exudate is fibrinous (croupous).
3. A form in which pus is produced.
4. A form characterized by hæmorrhagic exudate.

He considers these as progressive stages of one and the same kind of irritation, belonging to either of the three classes before named.

Applied to the study of repair of wounds, this doctrine taught that mechanical irritation (which caused them) alone was sufficient to explain the formation of pus, that it was unnecessary to seek further for its cause, and that tumefaction of the wound edges bears the same relation to failure to secure primary union that suppuration does to healing by granulation. This opinion seemed the more plausible since the wounds whose borders presented least tumefaction were those which healed most kindly *per primam*.

Attack upon this doctrine was speedy and determined. Cohnheim had published in 1867 his studies of the diapedesis of the leucocytes, and the importance of this publication, as well as its accuracy, were almost universally recognized; while the leading part heretofore played by the connective tissue corpuscle, according to Virchow's views, had now, at least, to be shared by the wandering leucocyte. This opinion has been since strengthened, to the point of conviction, by the labors of Cohnheim, Ziegler, and their scholars, so that now it is possible to find an explanation of such neoplasms as belong to the category of inflammatory, regenerative, hyperplastic or callus, in the known properties of the leucocyte.

I say it is now possible, even probable, but hold that as yet we are not in position to go to extremes. Cohnheim's enthusiastic followers claim that Virchow has considered innumerable cells to be descendants of connective tissue corpuscles, which are in fact escaped leucocytes. Even granting this, there has been no sufficient evidence yet adduced to show that the connective tissue cells are necessarily or absolutely passive, and take no part in cell proliferation. Consequently, it seems as if, in this controversy, the middle ground is certainly the safer.

But the attacks upon Virchow's dicta were made not alone by the histologists, but by those who, like Klebs, contested them upon etiological ground. By 1872, in Germany, the Listerian system had been pretty well adopted, and there no longer remained a doubt but that wound suppuration was caused by contamination of instruments, fingers, dressings, etc., with bacteria. Other infectious inflammations, *e. g.*, endocarditis, erysipelas, were correctly ascribed to microbes, and, in 1878, appeared Koch's masterly work on "Wound Infection." Now, the importance of mechanical, chemical and physical irritations, as agents producing suppuration, was lost in the overwhelming magnitude of the freshly studied "specific reaction (suppuration) due to a specific virus." To be sure, Virchow retorted, in 1880, that we did not know the exact nature of this specific reaction, and that it must be either chemical or mechanical, which is undeniable, yet it is equally undeniable that bacteria did not figure as irritants, when he so fully discussed the causes and consequences of inflammation, and that he remains to-day rather a skeptic as to some of the new teachings in this respect.

The introduction of the antiseptic method has effected both a revolution and a revelation. It was till lately held that the bacteria of putrefaction were also at the same time the pyogenic. In 1881 Virchow and his scholars claimed that suppuration was not invariably produced by micro-organisms and by them alone, but that when it displayed a milder form, less progressive, it was brought about by purely mechanical causes, fractures, wounds, etc. But the researches of Ogston, Rosenbach, Passet, and numerous other close and diligent observers, clearly demonstrated that suppuration has but one cause, that it is of parasitic origin, and that the pyogenic bacteria are not to be confounded with the saprogenic or putrefactive.

Studies directed especially to the elucidation of these hotly-disputed questions resulted in unexpected advance. Strassburger, Fleming and others found that the nucleation which precedes cell proliferation afforded an interesting subject by itself, and karyokinesis is now a well recognized link in the chain of cell progression. Not alone in the leucocytes is the karyokinetic process known; it has been studied in the connective tissue cells by Scheltema, Grawitz and Ribbert. This fact lends additional argument in favor of a position midway between the extremes of Virchow and Cohnheim. Whether the inflammatory irritant acts primarily upon the connective tissue elements, the capillary vessels, the muscular and the fatty tissues, whereby active hyperæmia and diapedesis of leucocytes are excited, or whether the reverse is true, will depend upon whether one sides with Virchow in the former case, or with Cohnheim and Weigert in the latter.

According to the views of the humoral pathologists, of whom Rokitansky was the father, pus corpuscles, which were seen in the exudate known to have left the vessels, were supposed to have originated from it, hence the definition of their day—"pus is dead blood." The ultimate cause of inflammation and suppuration was sought in the chemical condition of the blood; and the dyscrasiæ, or varieties of badness of the blood, were hence considered the causes of these phenomena. Although the old humoral pathology is now abandoned, it will be seen that it, nevertheless, took cognizance of certain truths, since such dyscrasiæ as diabetes, syphilis, and gout are well known to be predisposing causes of inflammation.

It was Virchow who decently interred this humoral doctrine, by showing that the formation of cells out of such exudates alone was impossible. By establishing the dictum *omnis cellula e cellulo*, he founded the new cellular pathology, which was to medical science what Keppler's laws were to astronomy.

Proliferation of cells now accounts for all tissue changes, though, by itself, it fails to supply all the knowledge of causes for which we earnestly yearn.

The misinterpretion of certain cellular phenomena by the cellular pathologists has been, in great measure, atoned for by the discoveries of Cohnheim and his pupils, who repeated, in every possible way, the observations first made in 1848, by Waller and Wallace, and who not only established the fact of the diapedesis in the leucocytes, but showed the vast importance of this process in explaining inflammatory action. If they, in their enthusiasm, claimed for their observations a solution of the whole question, they simply showed themselves human, and so liable to err.

While we are not, even to-day, in position to do more than calmly survey the fields where the pathologists of the recent past have excitedly contended for the accuracy of their own notions, yet we must admit that somewhat of truth was contained in the humoral doctrine, and that Virchow and Cohnheim are both right and both wrong; wrong, however, mainly in each trying to explain everything upon his own discoveries and in refusing to see as much of the truth in the teachings of his opponent as in his own.

The question may perhaps be legitimately raised whether it is possible to have acute abscess formation without the action of micro-organisms. The answer to this question should cover two different phases of the subject. First, it remains to be proven that sterile pus, providing it be ever met with, is really entitled to be considered pus, since it can in no wise be infectious, and since ordinary pus owes its principle characteristics to the bacteria which it contains. In the second place it does not necessarily follow, because no bacteria are found in pus at the time of its evacuation, that they were not present in the beginning as active agents. Thus Rosenbach examined the pus from two suppurating hydatid cysts, and found nothing, but that this is not usually the case is proved by the observations of several others. The pus from suppurating buboes following chancroid has occasionally been found free from organisms, and yet they are so nearly ever present in such cases as to imply an indisputable origin to such pus. Cheyne speaking of these cases states that such abscesses are doubtless caused by the virus of a chancroid, a virus which is in all probability of bacterial origin, but not yet recognized. If, however, we believe with Sturgis and some others that chancroid is not due to a specific organism but rather to a practical manifestation of the activity of known pathogenic forms, the explanation afforded by Cheyne will fall to the ground. In this connection he states that DeLuca has described a very similar coccus, which he considers the virus of soft chancre, and which he named *micrococcus ulceris.* This organism is a typical ærobe, and he explains the fact, if fact it be, that these buboes are not infected until two or three days after they have been opened, by the theory that it is not until after the access of air has been permitted for two or three days that this organism attains its full activity. Could this be proven it would furnish a strong argument against early or free incision.

As will be seen throughout these lectures I am endeavoring to make an actual difference between pus such as comes from an acute abscess under ordinary circumstances, and which is due to and contains micro-organisms, and another material quite similar to it in macroscopic and even in microscopic appearance, which contains no bacteria, which has no infectious properties, which is not capable of causing sepsis, which is not met with clinically and almost never except as the result of laboratory experiments, which is a fibrinous exudate more or less rich in cells and due to the action of powerful chemical irritants, but which is not pus in the true sense of the term. Such material, which we will call, if you like, *pyoid* or *puruloid*, can be produced by the aseptic injection of sterile croton-oil, or turpentine, or cadaverin, or of certain other chemical poisons, and has been noted under these circumstances by so many experimenters that it is scarcely worth while to catalogue their names. It does not undergo the fate of true pus, and while it may remain for a time enclosed within the tissues, it undergoes no spontaneous evacuation as an abscess tends to extrude its contents. Where bacteria are at work they by their peptonizing action readily dissolve this material and prevent the coagulation of fresh exudates and the absorption of the old. On the other hand where bacteria are not at work the tissues possess the power of dissolving and removing dead material, while such portion as cannot be removed is encapsulated and removed from further consideration.

(If any exception is to be made to the above statement it is with reference to cadaverin, which is stated by Grawitz and Scheuerlen to be not merely an irritant, but to prevent coagulation; but inasmuch as this is a ptomaine, we are, by its injection, reproducing, to a large extent, the conditions which would be furnished by bacteria if present.)

Grawitz has experimented carefully with *cadaverin*, which seems to combine the useful properties of an antiseptic and disinfectant with the undesirable powers of producing necrosis and inflammation. Two and a half per cent solutions destroy the pyogenic staphylococci after one hour's contact, and smaller proportions added to nutrient gelatine hinder or prevent their growth. Subcutaneous injections produce, according to their strength, necrosis, pseudo-suppuration or inflammatory œdema. In this pseudo-pus there are no pyogenic organisms. When five or ten per cent cadaverin solutions are mixed with pus cocci and then injected, the latter either die, or, as the injected fluid is reduced in strength by the tissue juices, they manifest their vicious propensities and cause acute phlegmons and abscesses. (*Virchow's Archiv.*, cx, p. 1).

Scheuerlen showed how solutions of cadaverin and putrescin, and various putrid substances, without aid from micro-organisms, could evoke a pseudo-suppuration; which nevertheless had nothing progressive or infectious about it. (*Fortschrit. d. Med.*, 1887, No. 23, p. 762). Fehleisen, however, showed that all these ptomaines possessed the property of delaying or preventing coagulation of the blood, and then repeated Weigert's statement that the suppuration is in large measure an affair of limitation of this process.

There is yet another material analogous to pus which deserves brief consideration here. I allude to the puruloid exudate upon the surface of granulating wounds. This material is physiologically different from that which an acute abscess contains inasmuch as it represents a useful product, at least the remains of a useful product, since for the repair of all tissues which heal by granulation there is necessary a certain amount of formative material, and this material can only come from pre-existing tissues, and must be supplied, at least in the main, from the blood. A quantity of leucocytes is constantly furnished to the granulating surface of which only a certain amount or proportion can be utilized. So many as are utilized undergo metaplastic changes, and become organized into tissue of a higher grade. Such of them as fail to be so utilized become the pyoid discharge from the healthy ulcer. Nowhere in connection with wounds is this fluid free from contact with the air, and consequently it is very likely to become infected on reaching the surface. If so infected it scarcely differs in any respect from true pus. If not so infected it will, nevertheless, show nearly the same constituents under the microscope, lacking only bacteria and necrotic shreds of tissue or debris. No granulating surface ever can cicatrize without the presence of a certain amount of this fluid. Unquestionably, however, irritating dressings or exposure to air, cause excess of discharge and infiltration of its cells.

In view of what has been said it will be seen that the true test as to the aseptic course of healing after a given operation or wound, is not so much as to whether any such puruloid material has been formed, but as to whether pathogenic bacteria have or have not been excluded. The typical aseptic primary healing of a fresh wound comprehends perhaps the absence of all puruloid discharge. Where, however, a drainage tube or drainage material has been introduced there will occasionally be found a few drops of gelatinous, creamy looking material upon the dressing, or obstructing the calibre of the tube, and this might easily give rise to the statement that such a wound had not healed, as enthusiasts claim it should under such dressings, without formation of a drop of pus. Some time ago, before I was aware of the investigations of others, I set myself the task of studying this matter in my own cases. It was at a time when I was using rubber drainage tubes much more than I do now in fresh aseptic cases. If upon the first dressing I met with any such material, cover glass preparations were made from it at once, and tubes of gelatine or agar were at the same time carefully inoculated with it. Subsequent observation of such cases has convinced me that while this material is not necessarily always sterile, it is quite usual to find it so, and that many a wound goes through a typical aseptic course, from which, nevertheless, a small quantity of such fibrinous exudate may come, this exudate being due apparently to the irritation caused by a foreign body, mainly the drainage-tube or even the suture material.

Quite corroborative of my own studies are the investigations of Bossowski who undertook the examination of fifty wounds which had been protected by antiseptic (iodoform) dressings. Each fresh wound was irrigated during the operation and at its conclusion with a 3% carbolic solution, and the iodoform gauze to be applied next the wound was soaked in 5% carbolic solution. Of the wounds thus treated only one fifth (20%) remained free of organisms. About one-sixth (17%) showed themselves contaminated by non-pathogenic organisms, of which the *staphylococcus gilvus* was most important on account of its resemblance to the staphylococcus pyogenes aureus and albus. About one-half the wounds revealed the presence of the staphylococcus albus, although the majority of them healed *per primam*. The number of these cocci was very small. The balance of these contaminated wounds (about a third) showed trifling or limited suppuration. The other wounds not including the above showed that staphylococcus pyogenes aureus, or streptococcus pyogenes were present, and they all were suppurating.

He is inclined to consider that the so-called aseptic-wound fever of Volkmann and Genzmer is due to the circulation in the blood of some of these bacteria or their products. He reminds us that V. Eiselsberg found pyogenic bacteria in the blood of feverish injured or operated patients; (*vide* above).

Bossowski also investigated the material contained in the drainage-tubes removed five to seven days after operation. He cut off a piece with sterilized scissors and dropped it into the culture-tube. He found that the pale reddish, somewhat translucent, thick clot which the tube sometimes contains, as well as the clear, serous, reddish fluid which often escapes, were free from bacteria. The softened, dark red or dirty yellow secretions and detritus usually contained organisms. Of course the plainly sero-purulent discharge always contained them. The researches of Staheli have also given about the same results.

After it was definitely understood that all surgical suppurations were of a parasitic origin, an effort was made to establish for the bacteria which caused them a property *sui generis*, as if they were neither chemical nor mechanical irritants, but possessed some hitherto unknown power. Such a theory prompted the investigations at once set on foot, during 1885-6, and conducted with most painstaking diligence by Hüter, Rosenbach, Orthmann, Lutton, and numerous others, to be referred to again, by which it was demonstrated that pure or sterile chemicals alone could never produce suppuration. Scheuerlen, Klemperer, Strauss, and others, have repeated these demonstrations, and have made conviction certain, that without bacteria or their products, suppuration never occurs. Some difficulty and confusion have arisen from the fact that it was found, in prosecuting these studies, that certain bacteria were pyogenic in the tissues of one animal, and not in those of another. Thus Grawitz and Dieckerhoff described a bacillus which thus varied in its effects according to the animal used.

In 1886, Grawitz and de Bary showed that very weak dilutions of pure cultures of the pyogenic bacteria (1 to 100, etc.), were resorbed without provoking suppuration. The daily use of ordinary solutions for hypodermic use is simply a homely illustration of this fact. They further showed that such active fluids as turpentine and strong nitrate of silver solution, which are of themselves actively parasiticide, when used upon certain animals in certain amounts, produced a fluid resembling pus. This fluid, however, contained no bacteria, lacked all the septic or infectious properties of true pus, and was produced under such conditions as never obtain, save in the laboratory of the experimenter, and at his pleasure only, at the expense of extreme precaution.

This is an appropriate place at which to stop, en passant, and ask whether it is fair to call such a fluid pus. Its like is not met with clinically, and the pus which we daily meet with, and which causes us so much trouble, is the pus which we particularly study, and which is particularly deserving of the name.

Moreover, aside from Grawitz' and Scheurlen's results after the injection of Brieger's cadaverin, it is, furthermore, quite probable that other ptomaines besides cadaverin, all of which are of bacterial origin, may be found to have a similar effect, though several, at least, have failed so far to evince it. Let it be well emphasized just here, however, that even these few substances which thus have been shown capable of producing this puruloid material, do so only under the most favorable conditions of time, quantity, and species of animal used for experiment. Weak ammoniacal and cadaverin injections are resorbed; those of greater strength are followed by watery or albuminous infiltrations, or, sometimes, by exquisite fibrinous exudates; used still stronger, they cause hæmorrhage and this pseudo-suppuration; and, finally, when used in full strength, necrosis and gangrene are the consequences. It seems to me, upon both theoretical aud experimental grounds, that this puruloid fluid, to which I have above alluded, may be properly considered the product of the death of the cells, resulting from the inflammation set up as a result of the injection of the irritant, and the liquefaction of previously solid tissues, and that it is entitled to be considered pus only in the sense that it is dead blastema; whereas we all know that the pus with which surgeons meet and contend is something more than dead or even dying blastema; that it contains, at least when active and septic or infectious, living and lively organisms, whose activity and properties are most pernicious. Here is beautifully demonstrated the accuracy of one of Virchow's observations, which were, in the main, brilliant and comprehensive, that tissue reactions or changes are not characterized by wide distinctions; that pus-production is not to be considered, by itself, as a distinct process, but only as a stage in the various possible inflammatory changes in connective tissue. Adopting this view, we see that the differences between the formation of this puruloid fluid and of pus, consist, in a pathological sense, in the penetration into the tissues of destructive germs, and, in a clinical sense, in the overwhelming pathogenic importance which the tissues and the purulent material now acquire by virtue of their presence and poisonous capabilities.

In clinical evidence of this feature, let me adduce the difference between an acute and a cold abscess. In the former the bacteria are still alive and actively producing poisonous material, in proof of which we have fever, sepsis, local destruction, even death. In the latter case, nature has thrown a sanitary cordon around the infected area in the shape of a thick investing membrane, the so-called but mis-named *pyogenic membrane*, inside of which the pyogenic bacteria have finally perished from starvation. These cold abscesses persist for months, even years, and may slowly disappear by well-known changes, while the patient presents few, perhaps no signs of fever, sepsis, nor of any trouble. In other words, so long as bacteria can live and migrate, the fluid in which they disport themselves is pus, true pus; the fluid of an old cold abscess is, according to this view, no longer pus. It was pus once; it is now *puruloid* in a second sense.

I have tried often to make cultures of pyogenic bacteria from this material and failed, for reasons just stated; so have many other observers failed, and our position in this matter is indisputably the correct one.

Garré has made a careful study of a number of cold abscesses, and with the exception of a few arising in lymph glands from which he could cultivate the staphylococcus pyogenes aureus, the only bacterial elements he could find were tubercle bacilli. These were with difficulty recognized by culture tests, but always by the result of inoculation. He contends that the view that pyogenic cocci had been present, but had been destroyed, can scarcely be entertained, since the pus out of these very abscesses could be used as a culture medium for the same pyogenic cocci, which could not be the case had their kind perished in it.

Garré concludes that so-called tuberculous pus is in reality not pus at all, but represents softened and separated necrotic caseous remains of previous tubercle elements. It contains mainly cell fragments and albuminated or fatty detritus, in contradistinction to the pus of acute abscesses which contains well formed pus cells.

The relative infrequency of tubercle bacilli in such pus, and the difficulty of recognizing them even by cultivation, or in any way save by inoculation, leads him to the hypothesis that this material owes its infectiousness rather to the presence of tubercle *spores* than to the adult bacilli, the former finding only in living tissues the condition requisite for their growth.

Garré's views as to the nature of tubercular puruloid are corroborated by Baumgarten, as well as by Terillon. (Prog. Med., 1887, No. 2.) (Deutsche Med. Woch., 1886, 34, p. 581.)

Tricomi, after investigations concerning the ordinary periarticular abscesses of tubercular joint disease, claims that so long as they remain closed they never contain pyogenic cocci, but only tubercle bacilli, if any. (Giorn. Internaz. dell Scienze Mediche, 1886, 6, p. 628.)

The conspicuous difference between the teaching of 1871 and that of to-day obtains in this, that the degree of inflammatory disturbance necessary for the production of pus is not produced by mechanical nor thermal lesions alone, nor by even chemical irritants, except under most peculiar conditions. All suppurations met with in practice are due to bacterial agency, but mainly when, through this agency, nourished within the tissues or planted upon absorbent wound surfaces, they propagate themselves and give forth their peculiar chemical products, *i. e.*, ptomaines. Still, even then, without some predisposing lesion or condition in animals and men, in tissues capable of resorption, the commonly known pyogenic cocci are innocuous.

To this fortunate fact it is due that not every wound suppurates which is not immediately provided with an antiseptic dressing.

While there is, virtually, no pus without bacteria, the reverse is not necessarily true; for we may have even pyogenic cocci present in relatively very small numbers without formation of pus. A careful study of these cases shows them to be those in which suppuration is imminent but not yet absolutely existant. For instance, there may be present a mild degree of swelling, with an albuminous exudate, all of which may be resorbed without pus formation. Whether we are to look with favor, or not, upon Metschnikoff's explanation of the disappearance of the relatively few bacteria present in such cases, is a matter which I hesitate to discuss, though, for my own part, I certainly think it offers a most attractive and reasonable explanation. Virchow's vivid picture of the "battle of the cells" surely loses nothing from Metschnikoff's treatment of the same subject, and phagocytosis is not yet disproved.

Virchow introduced the term "metastatic," and taught us what metastatic abscesses are, and the embolic process by which they are formed. This term also loses nothing of its significance in the light of recent enlargements of our knowledge. The emboli which cause them are themselves infected, or even individual germs may be transported *via* the blood current as most minute emboli, and the only uncertain or unappreciated feature of this part of the subject is the determination of why minute and metastatic abscesses appear in one place and not in another. This may be, in some cases, the result of pure accident. In general, it compels us to fall back upon the explanation of a *locus minoris resistentiæ.* This may be some mechanical lesion, perhaps one too minute for our vision, or some fracture or previous inflammatory focus. Points of least resistance certainly do exist, though what constitutes them such may be beyond our ken. No one can long study minute pathology without being convinced that there may occur a certain vulnerability of tissue, so to speak, for which we can offer no suitable explanation. The communication of contagion from one person to another is common evidence of this fact. Tissues, then, which suppurate are vulnerable in this respect: they succumb from not having the power to resist infection—that is, the invasion of their bacterial enemies, and the pus is the evidence of the conquest of vegetable cells over animal cells.

The matter is a difficult one to treat of. We have forms and forms of pus-formation. As Grawitz has shown, we have to deal with pus under at least four apparently different circumstances:

1. Cases of typical pyæmia.
2. Abscesses at points of least resistance.
3. Apparently spontaneous suppurations; *e. g.*, acute osteomyelitis.
4. Abscesses at points where there has been previously an inflammation.

He and Rinne have pointed out that the localization of pyogenic cocci is an affair of local determination, of interference with absorption, of chemical poisoning (through the circulation), of local ischæmia, etc.; in other words that by existing local irritations, by beginning inflammatory disturbances, or by regenerative cell-proliferations, in spite of previously held opinions, the metastatic grouping of cocci is absolutely prevented.

Rinne divides suppurations into two groups:

1. Those determined by bacteria of peculiar activity, whose attack upon the organism is vigorous; *e. g.*, tuberculosis, actinomycosis, epidemic cerebro-spinal meningitis, are caused by such organisms as seem to have a peculiar virulence, aside from any pyogenic properties.

2. Those determined by the members of the now well-known group of pyogenic cocci, particularly including staphylococci and streptococci.

We are confronted in this study by a most significant fact, which is very difficult of explanation. We have experimental proof that pyogenic cocci may be introduced into the tissues in no inconsiderable number—the same thing occurring every day in many accidental ways—that they may even be found circulating in the blood, without calling forth either suppuration or notable inflammation. According to the researches of Wyssokowitsch they do not escape by the kidneys. What, then, does become of them? It would appear, Grawitz says, that (*a*) they are dissolved, and disappear in the blood and other fluids; or that (*b*) there is an active conflict between them and the cells, a struggle for existence, which Virchow, as stated, has already called "the battle of the cells." The best known defender of the first view is Baumgarten, while Metschnikoff's name is most prominently associated with the second. Here again, there is really much to be said on each side, and there seems to be no reason why each may not be right. According to Grawitz the cocci usually die in pus after six to ten days, that is at a time when cell activity in the pus has ceased. Beyond a certain point increase of cocci is impossible in pus since the fluid becomes a too concentrated albuminoid material for them, just as syrups are too strong sugary solutions for the growth of fermentative and other organisms. On blood-clot they do not grow, though they will on blood-serum. Active penetration of cocci into white corpuscles is out of the question; therefore, when they are found in the interior of leucocytes, the latter must be regarded as the active agents. Certainly cocci are found inside the pus-cells, for anyone may see them there, and pus-cells, if we know anything about pus, were many of them originally leucocytes.

Certainly, too, one cannot say which he has to deal with, when isolated, a pus-cell or a leucocyte, unless he finds it containing one or more cocci imbedded in it.

If, then, in this battle of the cells, when once infection has taken place, the parasites are victorious, whether from overwhelming numbers, or from finding their enemies weakened from disease, then the infection of the surrounding tissues extends, and metastatic abscesses may finally or speedily result in the patient's death. On the other hand, if the tissue elements can successfully resist, then the battlefield is surrounded by a wall of young cell elements, which are very rapidly proliferated, and we have only a local abscess, in whose walls certainly takes place some of the phagocytosis which Metschnikoff has so successfully described. The course of that particular suppurative process is henceforth determined, not so much by production of some ptomaine, as by the reaction of the cell elements most concerned. So soon as the bacteria die or are killed, in case the pus has not been evacuated, the pus-cells undergo fatty metamorphosis, gradually disappear by absorption, or perhaps caseate in part; for an indefinite time there remains a concealed scar to mark the site of the old battleground, and finally all local and general damage is repaired.

The minute mechanism of abscess formation is of no small interest. Where infection occurs through the blood, the organisms are deposited in the smaller capillaries in the form of minute emboli, as is seen in pyæmia, and their first effect is the change in the tissues so well described by Weigert under the name of coagulation-necrosis. Sections through the periphery of such abscesses show that in immediate proximity to the central purulent mass there is a zone of tissue which takes no stain, and which presents a homogeneous translucent appearance, evidently resulting from the action of concentrated products of the micro-organisms, or from their own action, and constituting the coagulation-necrosis. If examined at the proper time a second zone appears outside this, which is composed of a dense mass of leucocytes, apparently collecting where chemical substances are more dilute and interfere less with cell life. The first zone becomes infiltrated on the one hand with cocci from the infected center, and on the other hand with cells from the outer rim, and, with the original tissue, rapidly disappears, probably largely owing to the result of the peptonizing action of the cocci. Meanwhile, for the same reason doubtless, the effused fluid does not coagulate, and thus we have a central collection of fluid containing leucocytes and cocci, that is, an abscess. When cocci spread into tissue after injection, or from infection of the skin, they usually at first follow the course of the lymph canals, and we find a central area of yellowish appearance containing leucocytes and cocci, surrounded by an inflamed area infiltrated with the same. The cocci, according to the density of the tissue spread in masses or singly, forming, in loose tissue, small groups or chains of a few individuals, the cellular elements swelling up and forming a homogeneous mass (coagulation-necrosis) ultimately undergoing liquefaction as before. Outside of this a zone of leucocytes is formed for the purpose of withstanding the onset and checking the progress of the micro-organisms. After a few days they usually get the upper hand, and the acute process is at an end. In the case of proteus vulgaris, which causes abscesses in rabbits, and of the bacillus of chicken cholera, which causes abscesses in guinea pigs, there is a mass of necrotic tissue in the interior of the abscess which is left undissolved on account of their feeble peptonizing power. The only difference, practically, between abscess and purulent infiltration is the circumscribed or indefinite boundary of the area involved. The principal difference between abscess and carbuncle is that in the latter there is no such perfect solution of dead tissues and cells. The coagulation-necrosis appears to involve such a mass of tissue at once that its solution and escape as pus is impossible. The bacillus of chicken cholera causes abscess in the guinea pig, and the proteus vulgaris causes them in rabbits, and in each case there is left a mass of necrotic tissue in the interior of the abscess whose solution has failed, perhaps on account of the feeble peptonizing power possessed by these organisms.

In man the chain of events is nearly the same as in the lower animals, save that they occur perhaps more quickly. The description above given refers more especially to abscess caused by staphylococci. The streptococci seem to have a slightly different method of action, and it may be that the differences between the two species are due, in some respect, to their varying peptonizing power.

Herein, too, we see the difference between recent and old abscesses, in respect to the so-called "pyogenic" membrane. The protective cell elements thrown out about an infected spot, as alluded to above, are a matter of hours, or, at most, of a few days' existence. No time is afforded for organization, nor is it desired. They are meant to serve only as a temporary barrier. Consequently, in an acute abscess we must not expect to find any such membrane, and, if it is folly to look for it, how much more so to describe it, as some have attempted to do. Only in the subacute abscess, or for some weeks pent-up collection of pus, can we find anything approaching it. But it is in the cold abscess, the long-existing one, *par excellence*, that we find a membrane or lining which can be peeled or stripped off; though it is a sad misnomer to call it a pyogenic membrane, since it is anything but this. It is the result of the organization and condensation of this zone of protective cell elements, which were thrown out when the infection and the encroachment were new, which was supposedly intended to be temporary, but has persisted as long as that encroachment from which it was originally intended to protect, and which has grown old and hardened in this service. It is no more pyogenic in the strict sense of the term than it is chromogenic, and its name should be dropped for a better term. If we must have a descriptive name for this membrane, and it is well that we should, I would like to suggest that we call it *pyophylactic*, as indicating clearly its function if not its appearance.

Pus proper comes to our notice in four ways:

1. In circumscribed subcutaneous collections of new formations—acute abscess.

2. From the surfaces of shut sacs and cavities—empyæmas.

3. On exposed tissue surfaces and granulating wounds—pyorrheas.

4. In the shape of purulent infiltration of subcutaneous tissues, more or less deeply occurring.

Pus proper, then, is a mixture of originally good cellular materials infected and gone to the bad, suspended in fluid more or less albuminous, and containing at times adventitious substances, like biliary or hæmic coloring matter, tissue shreds, etc.

When pus-cells have undergone fatty changes, when vital activity of all cells, parasitic or otherwise, has subsided, and when more or less of the fluid portion has been absorbed, leaving more concentrated, semi-fluid or solid residue—and when this has perhaps undergone caseous degeneration, then this material is not pus in the sense in which I am using the term, whatever it may have been originally. So long as it has the general appearance of pus, I would suggest for it the name *pyoid* or *puruloid.* When it is caseated, or is so thick that it does not flow, I would suggest that we then call it *archepyon*, that is to say, "originally pus."

I introduce these new names to you with considerable hesitation and with becoming modesty, yet I am convinced that if we had names for the different materials, or the different conditions of the same material, it would conduce to clearer notions concerning the substances themselves.

Certain conclusions based upon the above study may be formulated here, as follows:

1. Inflammation is, in effect, a disturbance of cell nutrition, along with cell proliferation, causing a recurrence to the embryological condition of certain of the cells of the tissue most involved.

2. This embryonal condition means a reversion to the form of those medullary or indifferent corpuscles, from which in the beginning of its normal development the tissue was built up.

3. Congestion, and even stasis, though they precede inflammation, do not necessarily cause it. They may subside before cell nutrition has had time to suffer. They may simply cause temporary cell activity.

4. Medullary, indifferent, or embryonic cells arise not only from the recognized cells of the tissue, *i. e.*, its active protoplasmic elements; it is probable that the intercellular or basis substance, which was originally produced from embryonic tissue, may again give rise to them.

5. When such new formed embryonic cells advance again

to the condition of basis substance, much of the inflammatory new formation has subsided. When with this is coupled restoration to the circulation of exuded fluids and such red and white blood corpuscles as are capable of return, and when all other newly formed cells are liquefied and absorbed, then the process of *resolution* is complete.

6. When both inflammatory and new embryonic cells establish a reticular intra-connection, then we have a true hyperplasia.

7. When into this collection of cells, parasitic vegetable cells (bacteria) are intruded, no matter how, blood-vessels break asunder, basis substance is dissolved, the individual animal cells are attacked, and these are now suspended in an albuminous fluid and represent pus corpuscles, and we have a collection of pus.

8. Pus-cells are no longer fit for any useful purpose, but constitute a source of offence. Henceforth they are treated as foreign bodies, of which the tissues endeavor to rid themselves at once. Nature extrudes them in the direction of least resistance, and hence we have the well-known phenomenon of the "pointing" of the abscess.

9. So far as we can learn, bacteria, and bacteria alone, can determine, in the human body, such a series of changes as lead to the formation of pus, *i. e.*, pus within the meaning to which I have endeavored to confine it. Whatever results may follow experimental introductions of a few chemicals into the tissues of some of the lower animals, such experiments find no parallel in our clinical experiences. Moreover, as stated above, the product of such experiments is not pus, but puruloid; it lacks the essential pathogenic and noxious elements of pus,—the micro-organisms which confer upon it its infective and toxic properties.

10. We are then prepared to make the brief and explicit statement that, *clinically* at least, we have no suppuration except such as is produced by bacteria; in other words, that pus is a product of parasitic origin.

LECTURE III.

PYOGENIC ORGANISMS.

SYLLABUS. *Pyogenic Organisms.*—Obligate and facultative. Staphylococci; consideration of their varieties and common characteristics.

Streptococci.—Identity of those of pus with those of erysipelas. Comparison of the general characteristics of the two genera and of their peculiar activities. Distinction between erysipelas and allied, yet clinically different forms of cellulitis, etc.

Bacillus pyocyaneus.—B. pyogenes fœtidus, etc.

Gonococci.—Included here, though not properly belonging here, since it is doubtful if they are truly pyogenic. Their relations to pus and to purulent mixed infection.

Pneumococci and Other Forms.—Bacilli tuberculosis, typhoid bacilli and other organisms rarely met with in pus. Table giving author's statistics of personal work.

A FEW years ago the known pyogenic organisms, or those which have the power of provoking the formation of pus by the destruction of exudate, could be counted on one's fingers. But the list now is greatly extended, and the organisms now known to be pyogenic belong to more than one genus,—belong not even in one kingdom, since they include both animal and vegetable forms. The former, however, pertain mainly to the lower animals, and man's worst enemies are principally bacteria.

While then it would appear to be impossible to give in exact detail the name or biological position of every organism that has the power of producing pus, those subjoined below are by all means the more common forms met with in it. There is every reason to believe that there is not one of the pathogenic microbes which may not have the power, at particular times or under peculiar circumstances, of producing pus, yet there are a limited number of forms which are so invariably met with in it and which so uniformly have the power of producing it if they exert any action at all, that they are grouped in an arbitary class under the name of pyogenic organisms. They are, of course, distinguished from each other, as are all other micro-organisms, by their microscopic appearance, peculiarities of growth, and their effects on animals. It has already been known for many years that organisms which, to the naked eye, in cultures, as well as when examined under the microscope, have every resemblance and appear to be identical, are yet capable of producing different effects in the living tissues. Possibly when our powers of observation shall be still further aided by some new device we may recognize some differences between them that at present we are unable to appreciate. For purposes of illustration, I have often put it in this way to students, that when we are at a distance from a crowd of human beings they all look alike to us, but that as we approach nearer we begin to notice differences of apparel and then of feature, so that we recognize friends or pick out strangers. So also one might tell the difference between two armies by the general color of their uniforms; and yet not be able to identify any particular organization. So it is in examining bacteria. Under the microscope alone all the pyogenic staphylococci appear alike. If we could get nearer to them, as it were, we might be able to distinguish between them. So, too, when we view an immense number of them on the surface of a nutrient jelly, we are able to distinguish one form from another by means of the particular color which they produce. The color of a culture by itself tells us no more about its distinctive organisms than does the color of an army seen at a distance, tell us what particular soldiers are engaged. We have certainly accomplished a great deal in the separation and identification of individual organisms, the final and crucial experiments in most instances being upon animals.

The wholly arbitrary yet clinically justifiable classification of *pyogenic* organisms would be into the *obligate*, that is those which always produce pus if they are given time and have any effect at all, and the *facultative*, which apparently only at times cause suppuration.

The Obligate.

1. *Staphylococcus pyogenes aureus*.—The staphylococci are so called because they tend to arrange themselves in the form of clusters. They grow easily at ordinary summer heat, but most rapidly above 30° C. When grown in gelatine this variety causes liquefaction with the development of an orange-colored precipitate. Grown upon agar there appears within twenty hours a whitish or light yellow opaque tint which soon becomes more distinct, and of a bright orange. It presents the same appearance upon potatoes.

2. *Staphylococcus pyogenes albus*.—This organism is very similar to the previous one in the character of its growth, and in its effect on animals, but it produces no pigment. Observers differ in opinion as to whether it is more or less virulent than the aureus.

3. *Staphylococcus pyogenes citreus*.—This grows like the former, liquefies gelatine, and produces a growth at body temperature which presents a light yellow color, indistinguishable at first from cultivations of aureus, declaring itself some days later. In each case this pigment occurs only on exposure to air. Where it grows along the needle streak, in agar, there is no color reaction. The pathogenic properties of this variety are probably milder than those of the two before mentioned, though all three are pathogenic; by which term it is meant that the results of injections or experiments in animals is death. An organism which when injected into an animal makes it sick only and does not kill it, is not considered by bacteriologists as pathogenic. It behaves in most respects like the aureus and albus. When cultivations upon solid media are covered with a layer of oil, Passet found that their bright lemon yellow color was not produced.

An exact estimate of the relative powers of these three forms can hardly yet be made. It has also been claimed that the aureus after transmission through the bodies of several animals becomes changed into the albus, but I do not think that this claim has ever been substantiated, while the distinction between the aureus and the citreus seems sufficiently well established. There is every reason to think, from clinical experience, that the virulence of the same species differs within wide limits at different times, since results are gotten with them at one time by one observer which cannot be repeated by others. This seems to be especially true of acute infectious osteomyelitis. A special staphylococcus of osteomyelitis has been described by some writers, but the opinions of those best fitted to express them concur in the belief that it is really identical with the staphylococcus aureus, differing only in this unknown characteristic of virulence. This group has been studied chemically as well as biologically. Passet made some investigations into the chemical activities of these three pyogenic varieties. He found that the gelatine which they fluidify has a neutral, not an acid reaction. This is probably a transformation of gelatine into gelatine-peptone. According to Brieger these forms give off ammonia, while the streptococci produce trimethylamin. All of the cocci which Passet found in abscesses, as well as pure pneumococci and the cocci of erysipelas, cause a curdling of milk.

4 and 5. *Staphylococcus cereus albus* and *flavus* are the names of two varieties identified by Passet. Each grows with a wax-like layer on the surface of gelatine, and in patches on potatoes. In the one case this layer is white, in the other of citron-yellow color. These two forms are met with occasionally in pus from the human subject, although I believe never alone. They are not pathogenic in rabbits, and in many other animals, and are not supposed to be in man. The surface of their growths has a particularly waxy sheen, while along the needle track they both form a grayish white streak with fine beads.

6. Babes has described and named the *staphylococcus flavescens*, which probably occupies an intermediate position between the aureus and albus. It liquefies gelatine, and its

growth on agar becomes yellow after about eight days. It is pathogenic for mice.

7. *Staphylococcus pyosepticus.*—Richet has described a microbe which he found in a cancer in a dog, and which he named pyosepticus. It is distinguished from the albus by its effects on animals. It both produces pus and fatal general infection. It has a short life, and grows best at 38° C. Below 25° fluidification of gelatine does not occur until the seventh day; this is later than occurs with the albus. Also in beef-tea cultures there are recognized differences. In rabbits it produces great œdema within twenty four hours, while the albus produces only the slightest infiltration. Later fever, emaciation and death result. Inoculation in the anterior chamber causes rapid suppuration and destruction of the eye. Death seems to be produced by a ptomaine, and in most rapid cases within from ten to forty eight hours. In dogs injections are followed by phlegmon, and high fever. Evidently it is much less virulent in dogs than in rabbits. Guinea pigs and doves succumb quickly. By vaccination with reduced cultures, animals are given an immunity from the virulent material. In the blood it seems to perish quickly In chronic cases it is found in colonies, especially in the liver. Experience with this organism in man has not been reported. (*Archiv. de Med. Exp.*, 1889, No. 5.)

Another peculiarity common at least to the pyogenic staphylococci is their wonderful vitality. They have the power of lying dormant in the tissues for months and years, and then of being aroused into activity by causes unknown, but such as accompany acute febrile or wasting diseases. Even in cultures they remain active for a long time. Old cultures emit a well-marked odor much like that of starch paste, and this odor can be frequently recognized in old dressings which have been saturated with pus. They more easily enter the blood current, and are by it more quickly disseminated. Phlegmons caused by staphylococci pursue a more rapid course both in time and in intensity of disturbance. There is no doubt at all in my mind but that collections of these organisms may hibernate, so to speak, in the bones, and possibly in other tissues, for twenty years, and then become again active, and exert sometimes a fatal degree of virulence.

According to all observers, the organisms which are most frequently met with in pus are the staphylococci, and of these most frequently the aureus, with the albus next. These are associated with acute abscesses, boils, acute osteomyelitis, etc., and their combination seems to be particularly unfavorable. Streptococci are also frequently present, but they are especially associated with erysipelas, or erysipelatoid processes, where suppuration occurs rather in the form of purulent infiltration, than from circumscribed abscess. They occur also, as was first pointed out by Ogston, in progressive gangrene, and are the chief or the most deadly organisms in pyæmia. Mastitis in women offers a good example of the different mode of action of these two species. Those mammary abcesses which are caused by staphylococci begin in the deeper part of the organ, and spread towards the surface, while suppurations which are caused by streptococci commence with an erysipelatoid affection of the skin, and extend from some crack or fissure of the nipple, the suppuration in the deeper part being secondary. The explanation is that the staphylococci act from the interior, spreading along the milk ducts, while the streptococci invade first the skin and spread along the lymphatic vessels. This statement is founded upon the demonstrations of Bumm, and is not theoretical.

Kitt has investigated similar disease in cows, and has cultivated a peculiar streptococcus from these cases, the injection of which sets up suppurative inflammation. In one case he injected pure cultivations into the milk ducts, with the result that in a few hours the corresponding portion of the udder became swollen, and by the next day it was acutely inflamed.

The clinical conclusions of Ogston, Rosenbach and Passet have been confirmed by Bumm and others, and may be stated about as follows: The staphylococci are the causative agents in primary and parenchymatous abscesses, while the streptococci are more disposed to excite peri-adenitis which shall terminate in abscesses. Bumm often found the former along with diverse non-pathogenic forms in fissures of the nipples, which do not accompany mastitis, and showed how they might thus penetrate even deeper and set up suppurative trouble. In at least one case he was able to demonstrate by sections, stained by Gram's method, that this had actually occured.

Okintchitz thinks that the staphylococci have a tendency to sectional localization about the joints especially in pyæmic cases, and that the streptococci manifest a predilection for cellular tissue. In this respect he takes a diametrically opposite position to Krantzfeld and Pawlowski. The staphylococci are so frequently found along with other pyogenic forms, that it is hard to assign them their exact role.

In 1886 Bonome described three cases of pulmonary tuberculosis in which he recognized staphylococci as the active agent in producing secondary suppuration, that is empyæma. In one case he recognized besides this form a diplococcus which he regarded as identical with Kleb's *micro sporon septicum*; so also in five cases of pulmonary gangrene he found them everywhere. On experimenting with pure cultures of the same germs made from these cases he succeeded in producing local gangrene at points of injection. He regards them as the active agents in causing the tissue necrosis, and holds the putrefactive features of these cases to be easily explained by the entrance of saprogenic organisms through the respiratory channels.

It has always been difficult, hitherto, to explain suppurative changes in the kidneys in scarlet and other eruptive fevers.

If we remember, however, that five years ago Fraenkel showed us how staphylococci were almost always to be found in the crypts of the tonsils, especially in cases of sore throat, it can readily be seen how they have ready access to the general circulation.

While, as we shall see shortly, there are differences of opinion as to the organisms most frequently concerned in producing pyæmia, and while the streptococci seem to be those especially to blame, we may as well mention here the results obtained by Pawlowski, who carefully examined five pyæmic cases. In one of these the metastatic manifestations were confined entirely to the joints. In this case he found streptococci alone. In the other cases he found staphylococcus aureus in the organs and soft tissues; results which tally well with those of Krantzfeld. One of his conclusions is worthy of repetition here: "These experiments lead me to the conviction that the staphylococcus pyogenes aureus is the active cause of pyæmia. For the development of the typical subacute form of pyæmia, there are required, indeed, beside the micro organisms, decided disturbances of nutrition, such as fractures and general circulatory lesions."

Evidently a great variety of disturbance may be caused by the same organisms, this being due to causes some of which are still obscure. Thus, the staphylococcus aureus may cause a dermatitis, a boil, an abscess, acute ulcerative endocarditis, acute infectious osteomyelitis, or even pyæmia; while the streptococci cause sometimes erysipelas, and sometimes peritonitis, mastitis, puerperal fever, and even pyæmia also. Their varying action is not alone due to the numbers in which they are introduced, nor yet necessarily the locality where they are introduced. That they do not of themselves always set up abscess formation is evident from the fact that they are frequently present in the blood, while as yet no abscesses exist. They are even excreted in a living state by the kidneys without giving rise to secondary abscesses. In almost all cases of septic fever they may be found in the blood, and yet it is known that such cases frequently run their course without abscess formation. In acute osteomyelitis they are found in the blood, although there is no suppuration outside the bone.

Rosenbach has reported the case of a woman, æt. 30, married 10 years, with four children living, and healthy when born. Her fifth child, born at term, was, nevertheless, dead at time of birth, though apparently alive until shortly before that time. Attention was at once drawn to the right leg, which was swollen and showed fluctuation. The whole leg had an erysipelatous appearance, and much pus was evacuated. It was thought there had been necrosis of nearly all the soft parts of that leg, as well as of the bone. This is of interest as showing that the organisms which cause this acute gangrenous process must have been introduced through the blood of the mother.

A case occurring very recently under my own notice was that of a newly born child who rapidly developed an acute osteomyelitis of the right leg and thigh, as well as an extra capsular abscess about one shoulder, and who lived but a very short time after the disease declared itself. To be sure there was the possibility in this case that infection had proceeded from the umbilical cord, and yet there was absolutely nothing about the part to lead to the slightest suspicion.

Babes concludes that there is a difference between ordinary puerperal fever, which he considers a streptococcus invasion, and pyæmia following abortion, which he has found due to the staphylococcus pyogenes aureus. (*Prog. med. Roumain*, 1889, No. 24).

Escherich examined milk from nine healthy women without finding bacteria in it; also from five women suffering from non-puerperal fever, such as phthisis, syphilis, etc., and found no bacteria. In thirteen cases of puerperal fever once nothing was found in the milk, once bacilli were present, once other cocci were found only in the milk from one breast, while in ten the same organisms were present in the milk from both. In none of these was there any excoriation of the nipple, nor abscess in the glands. Staphylococci were the prevailing organisms. He believed that in these cases the organisms entered the blood from the uterus and were excreted with the milk. Numerous other facts show that organisms may circulate in the blood without necessarily giving rise to local disturbances.

Garré's experiment to prove the active agency of staphylococcus aureus in producing phlegmons is now a matter of history. He inoculated a little wound at the border of the nail and in two days noted suppuration there. Then he rubbed into his arm, as if it were an ointment, a quantity of pure culture of the third generation, and in four days suffered from a typical carbuncle, with consecutive swelling of the lymph glands. Recovery was a matter of several weeks and of numerous scars. (*Fortschritte d. Med.*, 1885, No. 6.)

One such experiment, by the way, on man, is of more value than many negative results on dogs, which only go to prove their immunity, or at all events, their high resistence.

Aside from Garré's personal case of abscess following inunction we have Bockhardt's experiment upon himself. He introduced a minute portion of cultures of aureus and albus into the skin of one of his fingers. In forty-eight hours a small abscess had formed, and was opened, and from its pus he recovered the aureus. On another occasion he inoculated by inunction a portion of the skin of his forearm, about the size of a silver dollar. After having cleaned and disinfected it, and slightly irritated it with his finger nail, he employed the same mixture as before. Six hours after rubbing it in, the skin was reddened and painful; eight hours later a number of pustules had formed; these pustules contained the cocci which he had employed, and within a week they had dried up and disappeared. Some days later he repeated the experiment by rubbing in a cultivation mixed with a sterilized salt solution. Twelve hours later thirty-five pustules had formed; within five hours more he saw twenty-five more form, most of them being perforated by hairs. After a week all had dried up except two, which developed into large and painful boils, and for two or three months after he was subject to a recurrence of pustules upon the skin of the same forearm. The fact that Bockhardt's results were milder than Garré's was due to the fact that the former employed a much more dilute culture.

These pustules were of an impetiginous character, not being preceded by nodules or vesicles. These are such as Wilson defined impetigo to consist of, and may occur anywhere except where there is much hair. In such situations Bockhardt thinks that if the same cause acts sycosis will result.

In Wilson's impetigo he has always found streptococci, and he holds that the impetigo pustule is often a forerunner of a boil, for it is often seated on and precedes it. His views are corroborated by Zuckermann's investigations.

Bumm injected pure cultures of staphylococcus aureus into the subcutaneous tissues of his own arm, and the arms of two other persons. The cultures were mixed with a few drops of salt solution before injection. On each occasion a large abscess developed, whose pus contained large numbers of the same organism.

Schimmelbusch has demonstrated very beautifully how bacteria may work their way along the hairs into hair folicles and there cause furuncles. He rubbed into the unbroken skin (like Garré and Bockhardt) pure cultures of staphylococcus pyogenes aureus, by which pustules were produced. The skin was then excised, hardened in alcohol, its fat dissolved out with ether, then imbedded in celloidin, and sections made in series, which were stained by Gram's method and then with some contrast stain. A careful microscopical examination then showed that there was not the slightest injury to the tissues, but that the organisms had followed the hair shaft down into its follicle, and there proliferated, and that the infection of the tissues proceeded therefrom.

He found the same true of furuncles of spontaneous origin. The sweat glands do not have the same liability, since on the palm and the sole, where they most abound furuncles are most rare. On the contrary he finds them most common at spots where friction of dirty clothing or of ordinary soil is most marked; thus the back of the hands, the neck, the belly (from belts), etc. (*Archiv. f. Ohrenheilk.*, xxvii, 1889, 4, 252.)

8. *Streptococcus pyogenes—seu erysipelatis.*—By the term streptococci are meant those which arrange themselves in chains, sometimes of considerable length. They grow slowly on the ordinary culture media at a summer temperature, but at greater rapidity in beef tea and at body temperature.

On gelatine they form small, round, colorless colonies, which spread scarcely, if at all, on the surface. On agar they grow in small points but very slowly, and when sown on agar along a needle streak the growth is found, after weeks, to have extended but a very trifling distance. They do not liquefy gelatine, but in the absence of oxygen exert an energetic peptonizing action. When first described we heard considerable about two forms, namely: the streptococcus pyogenes, and the streptococcus erysipelatis. It is the latter which was so carefully and beautifully studied by Fehleisen, and demonstrated to be the active agent in the production of erysipelas. Observers are now pretty generally agreed that these two forms are identical. Individual cocci in any of these chains, of whatever species, are not necessarily of the same size. We have here another illustration of the fact already alluded to that the streptococci, which are so pathogenic in men, have very much less virulent properties in the lower animals. Fehleisen's coccus will not kill mice, rabbits nor guinea pigs. Moreover, it does not grow on the blood serum of calves, hogs nor guinea pigs, but only on the serum of rabbits among these smaller animals. Nor does it grow in the bodies of these animals. It must be said, however, that the attempt from these facts to formulate a general rule that cocci grow only in the bodies of animals on whose serum they thrive, would not be justifiable.

In the present connection we are speaking of the one form to which the two different names have been given. Although from eight to ten different sub-species of streptococci have been carefully studied, all of which grow alike and look alike, yet they possess widely different pathogenic properties. Thus the streptococcus which by some is alleged as the cause of diphtheria looks and grows like all the rest which have no such power. Thus too, Behring has identified a sub-variety which he calls the streptococcus *murisepticus*, because it kills white mice in from forty-eight to sixty hours. This, too, was isolated from diphtheritic membrane, and, except by experiment on animals, can not be differentiated from other forms. In beef tea they all grow precisely alike.

The view that Fehleisen's erysipelas coccus is entitled to rank as a true pyogenic coccus is confirmed by Hoffa, who found it in the pus from a knee-joint whose overlying skin presented an erysipelatous inflammation. According to this view it is not necessarily nor invariably pyogenic, but may act in this way. De Simone also has reported the case of true pyæmia following an unmistakable erysipelas, in whose metastatic abscesses a small coccus was found, which tends to corroborate the same view. He also lays stress on the many remissions of temperature met with in cases of pyæmia, as well as erysipelas, in connection with the fact that the streptococcus erysipelatis grows to best advantage at temperatures below 37°C., and that at 41°C., after forty-eight hours, in cultures, it dies. According to this view the high temperatures noted at times in clinical cases may be a conservative or eliminative factor.

Hajek, differing from Baumgarten and others, considers the streptococcus of erysipelas and phlegmon not to be identical, although they cannot be distinguished by culture differences, since he says the principles of growth in the living body are not the same. He studied two cases of erysipelas, which were complicated with intra-thoracic lesions. In one there was a sero-fibrinous pleuritic exudate in which he found a streptococcus having all the peculiarities of Fehleisen's. The other was a fatal case of so-called erysipelas-pneumonia, *i. e.*, pneumonia following erysipelas. In this case he found only Fraenkel's pneumonia-coccus. Fraenkel himself has quite recently made a careful study of the points of similarity between the streptococcus pyogenes or phlegmone, and that of erysipelas. He finds that neither morphologically nor in cultures, nor by color-reaction, can they be truly distinguished. He found the most beautiful growths in bouillon cultures. They behave alike in coagulating milk, and upon glycerine agar they grow alike. In experimenting upon animals no real distinction can be made, at one time phlegmon, at another lymphangitis, *i. e*, erysipelas being called out. In thus recognizing their virtual identity, he simply fortifies the position already taken by Bionde, Eiselsberg, Kurth, Winkel and others above quoted, and especially that occupied by Baumgarten in his large work.

Passet's studies concerning the retention of life of all these pyogenic cocci so far mentioned, agree very well with Rosenbach's, and are in accord with general experience. In jelly staphylococci will live a year or so, while streptococci do not last more than three months. Drying either of them on glass for ten days does not destroy their vitality. Even a heat of 99° C. for fifteen minutes does not certainly kill them.

The experiments of Schuetz in connection with the disease in horses known as strangles are significant. The disease occurs under two forms; it begins as a nasal catarrh, and in the milder form is followed by suppuration of the cervical and submaxillary glands, and of those around the pharynx. In the severe form metastatic abscesses occur throughout the body, and the animal dies of a form of pyæmia. On examining the pus from these abscesses Schuetz found a peculiar streptococcus constantly present. These he cultivated on horse-blood serum, and was able to reproduce the disease by injecting a pure culture into the nasal cavity. These organisms are also pathogenic for mice.

Aside from the streptococci above mentioned, Hueppe separated and cultivated still another form, which he met with in a case of puerperal fever. This organism formed typical arthro-spores, similar to those of leuconostoc, and did not grow in nutrient jelly, but did grow well on blood serum. It will thus be seen to have been specifically different from the ordinary streptococci. It hardly seems necessary to rehearse at this point or in this place, all the varieties of pyogenic streptococci. Enough has been said to show that they at least have many common properties, and that as yet we have really no accurate way of distinguishing between them.

In general it may be said of them that they possess even more virulent properties than the staphylococci, and, indeed, their presence in large numbers is in some degree an index of the violence and acuteness of the case. If it were permissible to argue by analogy of biological form and properties, a marked illustration of the severity of disease, called out by cocci which to a large extent resemble each other, might be found in such diseases of animals, as chicken-cholera, hog-cholera or swine-plague, rabbit septicæmia and, perhaps, some others. It is uncertain as yet whether these diseases can be inoculated at all upon man. They are at all events certainly acute and infectious enough in the animals mentioned.

General Remarks upon the Pyogenic Cocci.

Staphylococci and streptococci produce a peptonizing ferment by which albumen, even when coagulated, may be dissolved; and it is by virtue of this property that we have many of the phenomena attending suppuration. In milk they rapidly produce lactic acid, and this same lactic fermentation takes place sometimes in wounds, causing acidity of discharges, and in abscesses causes the well-known watery pus. (Cheyne). In our list of ptomaines produced solely in pure cultures of known species, we find none ascribed to pyogenic cocci; and they are not yet known to produce them; consequently fever attending suppuration can hardly be ascribed to this source. But, as Baumgarten suggests, it may be due to increased tissue change, due to their growth, the products thus formed being, perhaps, pyretic. Baumgarten supports this hypothesis by adducing the fever which occurs in trichinosis, where the question of ptomaines has not yet been raised.

Fehleisen is further of the opinion (*Arbeiten a. d. Chirurg. klin. Univ. Berlin*, III, 1887,) that the pyogenic cocci are not so much parasites in an actual sense, like anthrax bacilli, as agents for transportation of some injurious substances. He would explain the varying degrees of intensity of progressive suppuration and sepsis production rather by variation in strength or amount of the toxic material which they carry. In this matter he is decidedly opposed by those who believe these differences are to be explained rather by specific difference in activity which these organisms seem at different times to manifest. This latter view is borne out by analogy, since we see anthrax and tubercle bacilli evincing wide variations in specific energy under varying circumstances.

Okintchitz has carefully studied a number of cases of septic infection and pyæmia. (*St. Petersburg. Inaug. Dissert.*; Abstract in *Manchester Med. Chron.*) In his cases of so-called septicæmia he has failed to make the distinction between sapræmia and septicæmia which I shall endeavor to show is a legitimate and an important one, though he admits they deserve different names. In his cases of septic poisoning (*i. e.*, sapræmia) the patients' blood did not contain any pus microbes, though they were easily detected about the primary foci. But he did find in the blood of one of his septicæmic cases a peculiar microbe, which he considers identical with Bardoni-Uffreduzzi's *proteus hominis capsulatus;* in another he found Fraenkel's diplococcus and the staphylococcus pyogenes albus. In a number of cases of phlegmon he found one or other staphylococcus form (in a few of them in the blood), though only by culture experiments and not with the microscope. He shows, however, that their appearance in the blood seemingly has little connection with the intensity of fever or oscillations of temperature, and that the most pronounced clinical difference between the mycotic and the non-mycotic changes consists apparently in gastric disturbances, which are present in the former (mycotic) variety.

His pyæmic cases showed invariably either staphylococci or streptococci in the blood, which could ordinarily be recognized even with the microscope. Organisms thus found in the blood showed fission or reproduction very rarely as compared with those found in the pus of the primary foci, hence the supposition is justifiable that their reproductive activity is mainly confined to pus and not blood: hence also the great practical importance of thorough disinfection and destruction of primary and other foci. He considers that great numerical strength of hæmic microbes has a very unfavorable prognostic significance (*vid.* Eiselsberg's studies, Lecture, II), even in the absence of metastases about internal organs, the converse of this being also true. He thinks too that the bacillus pyocyaneus is rather a constant follower of the streptococcus, belonging more to the saprophytes, and invading soil prepared for it by other bacteria.

Manfredi and Traversa would seem to have discovered the explanation of certain peculiar symptoms, coma, cramps, etc., noted occasionally in severe cases of erysipelas. They experimented on numerous animals with bouillon cultures of the streptococcus erysipelatis which had been sterilized by filtration. They found that there were remaining in the solutions apparently two ptomaines, one having the property of producing paralytic pneumonia, the other of causing cramps and epileptiform convulsive movements. These ptomaines seemed best formed when oxygen was excluded, oxygen seemed to reduce them.

I have, for years, endeavored to find a pathological basis for the clinical distinction which an accurate diagnostician should make between genuine erysipelas, whose biological cause is well known, thanks to Fehleisen, and cases of what may be and often is called *cellulitis*, or perhaps the *erythema exsudativum multiforme* of Hebra.

I have made cultures and examinations from a number of these latter, and while I have never found such uniformity of results as would permit me to draw any permissable conclusions, so far as specificity is concerned, I can at least say that such cases as run a different clinical course are in all probability pathologically different. That is to say that I have never found erysipelas cocci when this disease failed to declare itself clinically. On the other hand I have found in these other cases sometimes nothing, and once or twice either staphylococcus forms or some organism whose identity I failed to make out.

This is quite in accordance with Cordua's studies. (*Zur Ætiologie des erythema multiforme, Deutsche med. Woch.*, 1885, No. 33, p. 576.) He investigated fifteen out of one hundred and twenty-seven cases of skin affection of the hand and fingers resembling erysipelas. Its resemblance as well as the fact that it was met with in patients peculiarly exposed, *e. g.*, cooks, butchers, oyster-openers, etc., led him to undertake the examination. From these fifteen patients he excised small bits of skin and placed them upon agar in the oven. From these he obtained a coccus resembling staphylococcus pyogenes albus save that it was three or four times larger. Upon animals it was inactive. He twice inoculated himself, with the result that at each point he produced a dark red swelling of the skin resembling the original disease. He likens it to Rosenbach's "*Finger-erysipeloid*" without establishing its identity therewith; and is rather of the opinion that different organisms may produce the same cutaneous disturbance.

Two years later in *Langenbeck's Archives*, 1887, Rosenbach more fully described the cutaneous disease which he termed *erysipeloid*, which appears much like Cordua's *erythema multiforme*. The microbe of this disease Rosenbach first supposed to be a coccus, but after studying it further determined that it belonged to the chladothrix group. It grows best on gelatine at 20° C., but very slowly, and in this medium it most resembles in growth the bacillus of septicæmia of mice. In form it is like the cladothrix dichotoma, but smaller. By inoculation of a pure culture Rosenbach produced an attack of erysipeloid upon his own arm.

Repeated endeavors to implant it upon lupous skin, in order to eradicate the specific ulceration, were fruitless.

9. *Bacillus pyocyaneus.*—This is the organism which occasionally gives to pus its greenish or bluish tint. It is one of the most active of the pyogenic germs, and up to the present has only been found in connection with man. That the organism is of some importance and interest to pathologists, is evidenced by the recent work of Charrin, "*La Maladie Pyocyanique*," which appeared in 1889. Ledderhose was among the first, perhaps the first, to establish that the bacillus pyocyaneus, which had hitherto been supposed to be simply a saprophyte, was in effect a pyogenic organism.

About the same time Pawlowski showed the same fact, and it was found that Koch had learned that it was fatal when injected into the peritoneum of the guinea-pig. While the statement above made, as to its never being met with except in man, is true, it nevertheless has powerful pathogenic properties when inoculated upon the lower animals.

Ernst has distinguished two varieties of this bacillus, which he denominates alpha and beta. They agree in morphology, but he has described a peculiar "chameleon phenomenon," which only the beta form presents in potato cultures. When such a growth upon a potato is disturbed with a needle, in from two to five minutes a change of tint is discovered, the reddish brown tone merging into a leaf-green. This seems to be so constant as to constitute a genuine point of distinction and to furnish a possible argument in favor of Naegeli's views concerning the mutability of species.

This organism, as it grows, generates a coloring matter which gives as characteristic a tint to cultures as to the pus, and which has been isolated by Fordos and been called *pyocyanin* (vide Lecture I.). This is a crystallizable substance; beside it another substance called *pyoxanthin* has been isolated by the same observer. Pyocyanin in alkaline solutions gives a blue, or in acids a red tint. A third coloring matter has been described by Babes, which gives by transmitted light a reddish brown, by reflected light an emerald green tint. It is soluble in water, and insoluble in chloroform. In acid solutions it gives a steel gray color. When these are made alkaline, the dichroism returns. It appears to be composed of two separate ingredients, one of which is soluble in alcohol, the other not. He also separated an aromatic substance whose odor reminds one of linden blossoms. These studies he made upon the beta form of Ernst. Pyocyanin is the most easily studied of these various substances, and is only mildly, if at all toxic. Minute crystals of it can be sometimes seen upon the surface of cultures. Its formation is not a regular nor a necessary accompaniment of the growth of the bacillus; it grows only under peculiar conditions, and the secretions of the skin appear to favor its formation.

10. *Bacillus pyogenes fœtidus.*—Passet found this organism in an abscess in the neighborhood of the rectum. It is by no means peculiar to peri-intestinal abscesses, however, since I have myself once found it in an abscess of the brain, and have met with it in abscesses from other localities. It is a short,

plump bacillus, which forms a white surface growth, and gives off a disgusting odor. On potatoes it forms a brownish mass. It does not liquefy gelatine. It grows in milk, but does not generate an odor. It is pathogenic in mice and guinea-pigs, but not in rabbits. The injection of a few drops of culture in the former animals causes septicæmia.

FACULTATIVE PYOGENIC ORGANISMS.

The gonococcus.—This organism figures, of course, most prominently as the sole cause of true or specific gonorrhœa. Discovered first by Neisser, it has since been the subject of a vast amount of study, of which the most fruitful part has perhaps been done by Bumm. He, more than any other, has demonstrated its specificity, and has stamped gonorrhœa as ranking among our best known parasitic diseases.

The gonococcus is a coccus, commonly met with in pairs, otherwise a diplococcus, presenting a double-biscuit shape or arrangement which of itself is quite distinctive. It is never found in chains, but frequently in tetrads, though it is not regularly thus grouped like the micrococcus tetragenus.

Nuclear stains, like the basic aniline dyes, do not make a deep impression on these cocci. Such stains as vesuvin or Bismarck-brown may answer well enough for cover glass preparations but do not suffice for sections. It is noteworthy, and in certain respects a valuable diagnostic point, that they loose their aniline stain when prepared according to Gram's method. While they share this peculiarity with certain other forms they may be differentiated from the pyogenic cocci by this sign, which consequently is of value.

Their most marked peculiarity is their power of penetrating living protoplasm and propagating there. Scarcely any, perhaps none, of the other pathogenic cocci have this property. In examining gonorrhœal pus the pus-cells will be seen to contain numerous groups of diplococci, which may have proliferated so rapidly as to completely fill the cell.

The gonococcus is well nigh the most difficut of all the common bacteria to cultivate. At first it was believed that the gonorrhœa-germ would grow upon the ordinary nutritive gelatine; then it was found that this was an error, and that they would grow only upon coagulated blood serum, or gelatine-serum, and furthermore that they thrive to best advantage only upon human-blood-serum.

It has been claimed that upon agar to which has been added 2 to 5% of Kemmerick's peptone they could be cultivated, but it has been found that this statement is not in accordance with fact. Also upon potato it can be scarcely grown. Even upon a suitable medium it is most difficult to cultivate.

It must be deposited in relatively large quantity and in pretty pure form. That is, if planted along with common pyogenic cocci they appear to prevent its growth. The temperature must be maintained at 33°-37° C. and new cultures must be made from day to day. The cocci die out in two or three days in cultures. Nevertheless Sinnety and Herneguy (*Progres Medical*, 1885, No. 33.) have shown that they may live inside the living body after the active disease has been apparently subdued by antiseptics; since in some of their patients they found the cocci a year after the apparent subsidence of the disease. The well known statements of Noeggerath are in perfect accord with these.

The investigations of Neisser, Bockhardt and Bumm make it indisputable that gonococci call forth an active purulent discharge from the mucosa of the genito-urinary tracts. They penetrate between the epithelial elements to the papillary layer. By the second day a lively emigration of the white corpuscles begins. The epithelial layer is thereby elevated from its base, and between them is formed a fibrinous exudate, exceedingly rich in cells, which later are loaded with cocci. Epithelial regeneration, in the average case, begins in four days and should be fairly complete in twenty. It appears that mucous membrane which is covered with cylindrical epithelium is most likely to suffer from this parasitic attack (urethra, uterus, glands of Bartholini, conjunctiva), while that provided with flat epithelial cells (mouth, nose) for the most part escapes.

According to Bockhart the acutest period of an attack of gonorrhœal catarrh is that during which there is the liveliest contest between the gonococci which have penetrated the mucosa and submucosa and the numerous leucocytes that are a part of the copious exudate which infiltrates the connective tissue.

The whole history of a gonorrhœal attack exhibits that we have to do with an irritative cause affecting a surface, as in the case of erysipelas, which in both cases commonly disappears without leaving permanent injury to the tissues; and that it is only exceptionally that the deeper tissues suffer, or those of internal organs by secondary localization. Such complications as epididymitis, endometritis or salpingitis are caused by spreading along continuous surfaces.

Bumm has done more than any one to study the nature of gonorrhœal mixed infection. The most common contaminating agents are the pyogenic cocci. Such mixed infections can take place in the female:

1. In Bartholini's glands. Here not only pyogenic but saprogenic cocci as well as the gonococcus can easily penetrate. Abscesses as well as retention cysts may occur here.

2. In the urethra. Urethral abscesses of either anterior or posterior wall occur by means of infection of the glands.

3. In the bladder. A true primary gonorrhœal infection of bladder epithelium is not known. The cystitis is of pyogenic origin and usually an extension from the urethra.

4. In the cervix. Suppurative parametritis is the analogue of acute gonorrhœal bubo in the male, which is always due to pyogenic action. Whether it is truly an infectious or an irritative process is yet an open question.

5. In the so-called gonorrhœal rheumatism (arthritis), which, as manifested especially in the knee, yields a fluid which shows a mixed infection.

6. Tubal-tuberculosis is probably often to be regarded as really a gonorrhœal mixed infection.

Indeed it is scarcely even doubtful whether such destructive lesions as those which lead to formation of stricture or suppurating bubo can be caused by gonococci alone; on the contrary it is extremely probable that these never occur without the participation of the common pyogenic cocci. The experiences of numerous observers, the writer included, show that the staphylococci are often to be found in the urethra, and such rare cases as one which I have elsewhere reported (*Jour. Cut. and Venereal Disease*, December, 1888, p. 441) show that pyæmia following gonorrhœa is not unknown, while the true pyæmia itself is not to be explained except by the action of the common pyogenic organisms. In fact one may accept the general statement that gonococci exert a true pyogenic action only upon certain mucous surfaces; and that beneath such surfaces they do not find the conditions necessary to their growth. They are ærobic in high degree, and it would appear that only epithelium and not connective tissue cells possess the required chemical character. Bumm found that injections of pure gonorrhœal pus into the tissues were harmless, as were also pure cultures. Indeed if 24 hours after injections of such material we cut into the part and remove some of this same pus we shall find that while pus cells still remain the gonococci have disappeared. This is a matter of great interest, showing that pus cells—apart from the bacteria which they contain, do not exert a pyogenic action. (Vid. Lect. II.)

Kitt has determined an analogous fact in connection with the mastitis of cows. The peculiar organisms only exert their pathogenic action when they are present in the ducts or acini of the gland, *i. e.*, upon its epithelial covering; if injected directly into its tissue they cause no suppuration.

Bockhart, in 1886, described a "pseudo-gonorrhœal urethritis" of moderate severity only, caused by a diplococcus that was met with also in vaginal secretion when it was *not* of acid but of alkaline or neutral reaction. It has nearly the same biscuit form as Neisser's coccus, is very small, is met with sometimes alone, sometimes in groups of two to six, usually in the fluid and not in the cells. It does not collect in such clusters as does Neisser's coccus. It grows on agar at 30°-32° C., but better on serum. Inoculation on the healthy urethra in two instances evoked a mild urethritis. In connection with this form of urethritis he describes also a "pseudo-gonorrhœal epididymitis."

Schwarz does not hesitate to express himself very positively that gonorrhœa is the only infectious catarrh of the female genitals; the bearer of the contagion, or rather the contagious element itself, is Neisser's gonococcus. Any secretion in which it is not found is not so. Without gonococci there is no gonorrhœa; all manifestations of gonorrhœa are connected with its activity; they are pathognomic evidences of the disease. (Die gon. Infection beim Weiber, *Volkmann's Saml. kl. Vort.*, No. 279.)

But this view of Schwarz fails to account for numerous cases of "bastard-urethritis" where inflammation runs high, where bubo is common, but where Neisser's coccus is not found in the pus. That these cases present sufficiently acute features will be attested by numerous patients. Whether these are provoked by Bockhart's diplococcus, or whether an acute urethritis can be engendered by staphylococci is not yet determined.

In the *Centblt. f. allgemeine Pathologie*, Vol. i, No. 18, Pellizzari has made a contribution toward corroborating the view that there is no real abscess produced by the gonococcus, but that all the suppurating buboes, and other abscesses appearing to be provoked through the influence of the organism are in reality mixed infections. He reports three cases of peri-urethral abscesses which appear to have been caused, as usual, by extension of the inflammation from the urethra into one or more of the urethral follicles, in all of which the pus proved to be a mixture. His paper constitutes interesting reading, and serves as a further corroboration of views already expressed.

The most significant other feature of true gonorrhœal disease is its occasional sequelæ in the shape of post-gonorrhœal arthritis, whose most conspicuous sign is an effusion into the joint cavity. This sometimes is a thin serum, and sometimes it is quite fibrinous or flocculent.

In 1885 I read that Petrone had recognized gonococci in this fluid. Soon after this I demonstrated this discovery by preparations from a patient of my own. Kemmerer, Affanasiev, Bergmann and Smirnoff, as well as others, have done the same thing. In view of such discoveries it would appear impracticable to explain these arthritides—or at least all of them—upon the ground of reflex irritation from the urethra, although there is no denying that we do meet with joint effusions after mere catheterization. Of course true suppurative arthritis is only to be explained by the theory of mixed infection already alluded to.

The pneumonococcus.—Two or three different organisms have been described under this name. That, for instance, of Friedlaender, which has a capsule, and that of Fraenkel which grows like Sternberg's coccus from saliva, and perhaps one other form. This organism certainly is not commonly pyogenic, but that it may prove itself so occasionally is placed beyond doubt by the investigations of several observers. For instance, Fraenkel, like Talamon and Salvioli, has found his pneumonococcus in cases of empyæma following pneumonia, and has come to the conclusion that this sputum-septicæmia coccus is a common and frequent cause alike of pneumonia and of these subsequent diseased conditions. It concerns us most in this relation to know that under certain circumstances it may show a true pyogenic activity. It has also been found in pus from cases of combined pneumonia and meningitis, the intracranial pus being found to be a pure culture of the microbe. These statements are corroborated by Foa and Bordoni-Uffreduzzi.

Gabbi and Puritz have identified the diplococcus of Fraenkel in the pus from a peri-articular abscess occurring in a case of acute pneumonia. Pus from this abscess injected under the skin of a rabbit produced acute septic symptoms, of which the animal died. In its blood the same coccus was also found. This appears to be the first case of peri-articular inflammation recognized as being caused by Fraenkel's pneumonia coccus. Hitherto only cases of arthritis have been described by Weichselbaum, Belfanti, Monti and Santer, all of whom have found it in pus from the interior of joints in complicated croupous pneumonia. (*Centblt. f. Bakt.*, viii, No. 5.)

Injections of it into the knees of animals have almost invariably produced purulent arthritis. After injecting cultures into neighboring tissues, and then injuring the joint surfaces with sterilized needles, thus making a point of least resistance, the results were less certain though frequently successful. Gabbi compares the inconsistency of these results with the great infrequency of joint complications in pneumonia. Weichselbaum found this same coccus in three cases of peritonitis. In one of them it followed a pneumonia; in the second a double pleurisy; in the third it was idiopathic. It will be remembered that Fraenkel's coccus is the same as the *micrococcus Pasteuri* of Sternberg.

In the early part of this century it had been noted by Dr. B. W. Dudley, of Kentucky, that during an epidemic of typhoid pneumonia which devastated the central portion of his native state many cases were followed by a "bilious fever characterized, like the plague, by a tendency to local affections. Abscesses formed among the muscles of the body, legs and arms, and were so intractable that limbs were sometimes amputated to get rid of the trouble."

The pseudo-pneumonococcus of Passet.—He found an organism in the pus of acute abscesses, which closely resembles Friedlaender's pneumonococcus. He met with it once in a small acute abscess of the back, and once in pus from the knee joint of a patient who sickened and died of croupous pneumonia. In the former instance he found it alone, in the latter in connection with other organisms.

It forms grayish-white, semi-circular elevations on the surface of gelatine, and in the earlier stages of growth is indistinguishable from Friedlænder's coccus, but at a later period recognizable differences appear both as regards growth and effect upon animals. In pure cultures it does not grow along the needle streak, hence it is ærobic. On potatoes it gives off no gas, and mice inhale it without disturbance. Injected into the pleural cavity of mice and rabbits, it causes pleuritis. When injected subcutaneously it often produces abscesses in mice and rabbits, while Friedlænder's coccus is not pathogenic for rabbits.

Micrococcus pyogenes tenuis.—This was first described by Rosenbach, who found it in three cases of deep suppuration. Since he described it not a single observer has met with it till Dr. Maria Raskina, of St. Petersburg, succeeded in isolating it from the pus and organs of an infant dying of severe scarlatina, complicated with pyæmia, on the 18th day.

The pus from the metastatic abscesses was found to be almost a pure culture of this coccus, while the parenchymatous juice of the various organs contained beside it a large diplococcus of unknown biological position. Inoculations of pure cultures of the pyogenic coccus under the skin of rabbits gave negative results, though the blood of the animals showed the presence of the coccus for at least twenty hours after injection. Hence the true pyogenic power of the organism is somewhat problematical, Rosenbach's researches failing to demonstrate it. Dr. Raskina considers that it may belong to the group of so-called *metabiotic* microbes of Garré; that is that it occurs only secondarily after suppuration has been caused by some other coccus. Nevertheless she states, as above, that the pus from her case seemed almost a pure culture of this same organism. (*Trans. of the Third Gen. Meeting of Russian Physicians,* 1889; Abst. in *Manchester Med. Chronicle.*) On agar it forms an extremely delicate, well nigh invisible layer. The individual organisms are somewhat irregular in shape, and average larger than the streptococcus pyogenes.

Rosenbach's oval coccus.—This observer found in one case of acute suppuration an oval coccus, which rapidly liquifies gelatine, and produces pus when injected into the eyes of rabbits. It has not been further studied, nor even given a name.

The glanders bacillus (*Bacillus malei*).—Rudenko after carefully studying the lymph glands in cases of lymph-glanders produced abscesses by injection of pure cultures of glanders. The pus from these abscesses he also found to be a pure culture of the injected microbes. Consequently we must include this organism among our pyogenic forms. He always found the neighboring lymph glands to be infected with them.

Bacillus of malignant œdema (*Vibrion septique*).—Whether the bacillus of malignant œdema really deserves to be grouped with pyogenic organisms, is not yet known. It has been found in pus, however, as, e.g., a very interesting report by Braatz shows.

In a case of progressive gangrenous emphysema of the cervical region he evacuated a quantity of very offensive, gaseous, seropurulent fluid. In this fluid the bacillus was found along with staphylococci and streptococci. The most interesting feature of this case is that the patient, an ignorant peasant, had a swelling under the jaw first, and then, by advice of his wife, drank a glass of chamomile tea in which he had put a tablespoonful of rat fæces. When we remember the liability of the rat to this disease we seem to see an explanation for the development of the same in man.

The bacillus tuberculosis.—This organism is not commonly enumerated as among the pyogenic, yet it is indisputable that it can produce abscesses whose contents are pure cultures. Thus, for instance, Fraenkel has carefully reported a case of brain abscess in whose contents the tubercle bacillus was the only organism found. That such collections of pus were not originally mixed infections is apparently proven by the fact that they become infected with pyogenic organisms so soon as they became exposed, as by incision.

It is hardly credible if one group of staphylococci, for example, had exhausted the fluid contents of such a cavity and then died out in it, that another group could later live and thrive in the same fluid. Fraenkel's deduction was warmly contested by Baumgarten, who claimed that he did not prove his case, that he no doubt had a tubercular focus in the brain, but that its detritus was not true pus, but pseudo-pus, consequently that the tuberculous bacilli were not entitled to be considered as truly pyogenic. However Baumgarten's objection must fall in the light of the reasoning above given. Whether such organisms as the tuberculosis bacillus shall produce abscesses or not is largely a question of time. In virulent *milzbrand* the poisoning of the system is too rapid, and the animal dies before the anthrax bacilli have time to act, but when a Guinea-pig is inoculated with attenuated virus, and then dies six, eight or ten weeks later, one finds not only infarcts and metastatic processes, but multiple abscesses whose contents are pure cultures of anthrax bacilli. The same is known also of the typhoid bacillus, of the pneumonococcus, of the bacillus of tetanus, and this general statement also holds good for tubercle and for septicæmia. We have *foudroyante* forms where the specific element kills before abscesses have time to form, and we have other slow forms with the well known abscesses. In all these cases it is not so much a question of the pyogenic powers of certain bacteria, as of the time during which they are permitted to act. The bacillus of tetanus, for instance, is never found without the presence of pus, so far as I know, at least in the human organism, yet its main influence lies not so much in its pyogenic as in its tetanizing powers. The bacilli get into the divided cord of the new-born from the midwife's rusty shears, or dirty hands, or from the dirty rags bound around it, and the tetanus of the new-born in no sense differs from the traumatic forms.

Tetanus bacillus.—Inasmuch as it is proposed to devote a good portion of Lecture V. (q.v.) to this organism, it will be unnecessary to do more than to simply mention it here as among the facultative pyogenic species.

Typhoid bacilli.—When, later in this course, I shall, as I hope, take up the topic of *Mixed Infection,* I shall have more to say upon these bacilli as pyogenic organisms. Golzi had opportunity to observe a case of acute osteomyelitis during the course of a relapse of typhoid fever, and in the pus found typhoid bacilli and no other organisms. He then experimented with pure cultures of bacilli, and found that if he first broke the femur and then injected them he determined an abscess at the seat of fracture nearly every time. He concludes that these organisms are much more disposed to produce suppuration in rabbits than in man. (*Lo Sperimentale*, June, 1890).

Orloff has devoted no little time to a careful study of the suppurations which complicate typhoid. (*Centrlblt. f. Bakteriologie*, 1890, viii, No. 12, p. 366, from *Wratsch.*) They occur most frequently in the skin-boils, in the subcutaneous areolar tissue-abscesses, particularly when there are pressure-sores; also as abscesses of the larynx in the connective tissue around the trachea and in the mediastinum; less often in the muscles (rectus abdominalis and glutæi), the more external lymphatic glands, the thyroid and salivary glands and the bones and joints. The latter terminate sometimes in diastasis, and sometimes in exostosis or suppuration. Sometimes one bone or joint suffers, sometimes several; more commonly in younger patients. The exudate is sometimes serous, at others sero-purulent or absolutely purulent. Of internal suppurations perhaps the more common is empyæma, though abscesses occur in liver and spleen; these suppurations are not grouped with disintegrations of mesenteric glands, nor with rupture of splenic or ovarian infarcts.

Investigators generally incline to the view that most of these suppurations are really mixed infections, though undoubtedly typhoid bacilli alone may provoke formation of pus.

But Orloff decided to settle this matter by a series of experiments which could not be mistaken. He undertook (1) to determine by injections of pure cultures whether typhoid bacilli could call forth pus; (2) whether, if so, it was by virtue of their own presence or by their products, and whether, if not, the injection of mixed cultures produced any modification by action one upon the other. These experiments appear to have been conducted with most scrupulous attention to details, which, however, it is hardly necessary to describe just here. His conclusions were carefully deduced from amply sufficient data and bear the stamp of reliability. They are:

1. Injections of typhoid bacilli (pure cultures) into various tissues (joints, muscles, etc,) produce active round-cell infiltration and violent suppuration.

2. The same results, though much less acute, follow injections of sterilized cultures; whence follows that:

3. The chemical products of these organisms are, at least in no inconsiderable degree, the causes of these manifestations.

4. Suppurations occurring during typhoid or during convalescence, whose pus contains only typhoid bacilli, depend entirely upon them for their provocation, and are not to be regarded as mixed infections.

Further confirmation of this view comes occasionally also from yet other sources. Thus, Achalme (*La Semaine mèdical*, 1890, No. 27) reports a case of periostitis of the tibia as a sequel of typhoid. Typhoid bacilli were found in the pus and no other organism.

Micrococcus tetragenus.—This is an organism from the mouth, known to be present in pulmonary abscesses in consumptives, as a contamination. So far as I know the first recognition as a form which *per se* could produce pus was a case which I reported in *The Medical News* in 1888. It occurred in a young woman with a peculiar form of submaxillary and cervical phlegmon of exasperatingly slow course, in the pus from which I found this coccus and this alone, and in which the path of infection from a badly diseased tooth could be traced.

It is known to possess pyogenic properties in certain small animals.

Zuckermann, writing in 1887, condensed the results obtained from a study of 495 acute abscesses. According to these staphylococci were found in 71%, and streptococci in 16%. In $5^1/_2$% both were found together. In the balance of cases other forms were found. These results vary but little from the more recent studies of Steinhaus.

Some two or three years ago I presented to the American Surgical Association a table showing my findings in about 50 purulent cases. I have since more than trebled the number, but present herewith a table of only 100 cases, in which, among other things, will be found, *e. g.*, my justification for some of the statements made in the previous lecture. (Absence of organisms in the archepyon of cold abscesses, etc.) These 100 cases are selected only in this respect, that I am prepared to vouch for the accuracy of the results; which we cannot always do. (See Table).

Anthrax bacilli.—These, as a rule, especially in man, do not alone provoke suppuration, but abscesses which contain them appear to be the result rather of mixed infection.

But there is some reason to think that even in man, and much reason to believe that in animals they may, exceptionally, act in a purely pyogenic capacity.

Actinomycosis.—Pathologists were for some time in doubt as to whether actinomycotic abscesses were not all truly mixed or secondary infections. This matter I believe is now set at rest, and it is definitely settled that rarely these fungi provoke suppuration without aid from other organisms.

Szénásy, in the first case of actinomycosis recognized in Hungary, met with a painful fluctuating swelling of the right mamma. By aspiration he withdrew tenacious pus in which were found typical actinomycotic forms; which were also found in the sputum. (*Centblt. f. Chir.*, 1886, No. 4.)

TABLE.

Disease.	*Number of cases*	*Staphylococcus pyogenes albus*	*Staphylococcus pyogenes aureus*	*Staphylococcus pyogenes citreus*	*Staphylococcus cereus albus*	*Staphyloc'ccus cereus flavus*	*Streptococcus pyogenes*	*Bacilus pyogenes fœtidus*	*Micrococcus tetragenus*	*Streptococcus erysipelatis*	*Bacillus fluorescens liquefaciens*	*Bacillus anthracis*	*Bacillus fluorescens putridus*	*Bacillus uræ liquefaciens*	*Bacillus of green pus*	*Bacillus coli commune*	*Bacillus pseudo-pneumonicus*	*No growth*
Abscesses	32	15	21	2	5	.	2	1	1	..	..	..	1	..	..	..	..	..
Caries	3	2	2	..	1	1	1	..	..	..	..	..	..	..	..	..	..	..
Necrosis	7	3	4	..	1	2	..	..	..	..	..	..	..	..	..	..	..	..
Ulcers	4	2	..	..	2	..	2	..	..	..	1	..	..	..	..	..	..	..
Ulcer, syphilitic	1	1	..	..	1	..	1	..	..	..	..	.	..	..	..	..	..	..
Chancroidal pus	2	..	1	.	..	1	..	.	..	..	..	..	..	1	..	..	..	..
Pus from bubo	4	3	..	1	.	..	1	..	..	..	..	..	..	..	1	..	..	..
Discharge from chronic gonorrhœa	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Pustules	5	2	4	..	..	..	..	..	..	..	..	..	..	..		..	..	..
Carbuncle	3	1	1	..	..	..	1	1	..	..	..	1	..	..	..	..	..	..
Phlegmon	1	1	..	..	..	1	..	.	..	..	..	..	..	..	..	..	..	..
Cellulitis	1	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Erysipelas	2	1	..	..	..	..	..	..	..	2	..	..	..	..	..	..	..	..
Felon	1	1	1	2	..	..	..	..	..	.	..	..	..	..	..	..	..	..
Empyema	6	1	2	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..
Gangrenous phlegmon	1	1	1	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..
Tetanus	3	3	1	..	1	..	1	..	..	..	..	..	..	..	..	..	..	..
Pyæmia	1	1	..	..	1	.	..	..	..	..	..	..	..	..	..	..	..	..
Hypopyon	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Gall-bladder abscess	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..
Abscesses, cold	9	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	9
Hæmatoma, material from	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
Tubercular testicle	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
Tubercular lymphnode	2	..	..	..	..	..	..	..	..	.	..	..	..	..	..	..	..	2
Enlarged thyroid	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
Central osteo-myelitis	1	..	..	..	..	.	..	..	..	..	..	..	..	..	..	..	..	1
Tuberculosis of bone	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
Post-operative sarcoma	1	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..
Total	100	41	38	6	12	7	11	2	1	2	1	1	1	1	1	1	1	18

The writer must here express his indebtedness to his previous assistant, Dr. Matzinger, and his present assistant, Dr. Bergtold, for most of this work.

Aspergilli.—The same is true of two varieties, at least, of aspergillus; and it is claimed that spirochæte may provoke suppurative otitis media.

In 1877 Grawitz described a purulent inflammation in rabbits' eyes which he had experimentally created with this fungus. In 1881 he injected it into rabbits' blood and subsequently recovered it by culture methods from the liver, kidneys, etc., and demonstrated for the first time that it might act as a pure pyogenic organism.

And were we considering suppuration in animals rather than in man we should have to include such microbes as those which cause contagious acne in horses, the various septicæmiæ in different animals, etc.

Following I purpose to mention, without attempt to classify them specially, several forms of organisms which have been met with in pus from various human sources. In 1885 Tilanus reported two cases of compound fractures of the leg, which ended in gangrene. From the gangrenous tissue of one he separated a new bacterium which he termed *bacillus gangrenæ;* from the second another, to which he gave the name *micrococcus fœtidus.* After experiments therewith and failure to get any inoculation results, he regarded them as saprophytes, rather than pathogenic microbes, which, nevertheless, generated the ptomaines by which the patients were fatally poisoned.

Kartulis has found in fresh pus from abscess of the liver consequent upon dysentery, the dysenteric amœba which he had previously described as having been found in cases of acute and chronic enteritis among the Egyptians, but along with it were found the common pyogenic cocci, and he makes no claim that the amœba had anything like a pyogenic action. This naturally calls to mind the recent discovery of Prof. Osler, who has, within a year, reported a number of observations on pus from hepatic abscesses in which could be still seen active and moving amœboid organisms. Enough study has not been given to these, so far as I know, to permit a statement as to whether they are or are not in effect pyogenic organisms, though I presume that they are.

A few years ago Netter determined that after ligature of the ductus choledochus, the previously sterile contents of the gallbladder contained bacteria, and by ordinary methods he made out two species of organism, one the well known staphylococcus pyogenes aureus, the other a short bacillus, which he, for the first time, described, and which he identified as the same which he and Martha found in an hepatic abscess consequent upon gall-stone (*Archives de Physiol. norm. et pathol.* 1886, No. 5, p. 7). This case was complicated with ulcerative endocarditis, and the same bacillus was found in the cardiac valves. They regarded it as an inhabitant of the intestine which wandered into the gall duct, favored by the obstruction above, then into the liver tissue, and thence into the blood, causing both the abscess and the valvular lesion. They found, furthermore, in literature five other cases of combined biliary obstruction and verrucous or ulcerative endocarditis, and they consider that this bacillus possesses possible pyogenic properties.

Netter, in this latter communication, claims that hepatic abscesses, caused by staphylococcus alone, are accompanied by others in other organs, while those caused by his peculiar bacillus are marked by a lowering of temperature, even to 34° C., and cellular changes in the liver. In mixed infection we have a combination of symptoms. Injections of staphylococcus cultures produce the now well known pyogenic effects; injections of cultures of his bacillus caused disseminated, hyaline degeneration of liver cells. He has also met with this bacillus in the biliary passages of another patient after biliary obstruction, without abscess, beside the case reported by himself and Martha. (*Progrés Médical*, 1886, Nov. 13. p. 992.)

It occurred to me last winter to meet with a case of abscess of the gall-bladder from which I removed 104 gall-stones, in the pus from which I found a bacillus which tallies in every respect, so far as I can learn, with that described above by Netter; having only Netter's somewhat vague description to go by, I am unable, positively, to identify it as the same, though I have no doubt of it.

Hauser (*Ueber Faulnisbakterien und deren Beziehung zur Septicæmie*, Leipzig, 1885) describes three forms of saprophytic bacilli, which he terms Proteus vulgaris, Proteus mirabilis and Proteus Zenkeri. They are characterized in part by a certain pleomorphism, which he, perhaps, unduly exaggerates, and by a peculiar "schwarmstadium," by which is meant that in 5% gelatine they make sudden and extensive changes of locality, that they *swarm*, as it were. That they are certainly saprophytic in action, he placed beyond a question. He further showed that they produce a very active ptomaine, which, in small quantities, exerts a marked toxic effect, causing in living animals all the phenomena of putrid intoxication, increased pulse and temperature, emesis, cramps, cyanosis, collapse and death. That they possess pyogenic properties is not demonstrated. It, moreover, appears that they are not harbored nor nurtured in the living tissues and fluids of healthy animals.

Chantemesse examined carefully a few cases of Delhi boil ("*bouton du Nil*"), and isolated a coccus which, in many respects, resembled the staphylococcus pyogenes aureus, but which was slower in liquefying gelatine and more quick to assume a yellow tint, and which grew a little differently on potato.

Inoculated upon two human arms, in pure culture, it produced each time a furuncle, which changed to an ulcerating nodule, the ulcer being crateriform, and rapidly healing under sublimate dressings. The pus from this furuncle was a pure culture of this "microbe du clou du Nil." Upon rabbits it was sometimes rapidly fatal, sometimes produced chronic lesions, resembling those upon men. (*Annales de l'Institute Pasteur*, 1887. No. 11). This must be consequently reckoned as one of the pyogenic forms.

Netter investigated twenty five cases of suppurative meningitis. Four times he could trace it to aural disease, once each to the sphenoidal and ethmoidal cells. In eleven cases it was metastatic, the primary focus being twice in the placenta, once in the pleura, and eight times in the lungs. He found the following bacteria which he considered as the active agents in producing the suppuration:

Diplococcus pneumoniæ in sixteen cases.
Streptococcus pyogenes in four cases.
Diplococcus intracellularis in two cases.
Bacillus pneumoniæ (Friedlaender ?) in one case.
A short mobile bacillus, identical with that found by Newman and Schaffer in meningitis, in one case.
A small curved bacillus that could not be cultivated, in one case.

He consequently maintains that suppurative meningitis can be caused by *various* bacteria, whereof the diplococcus pneumoniæ is most common. He, further, thinks it possible to distinguish the bacterial factor by the clinical course of the disease, and the character of the exudate. When the diplococcus pneumoniæ was found the exudate was green and viscous; when the streptococcus was found it was less adherent and more sero-purulent.

Other investigators have found the diplococcus pneumoniæ in twenty-seven cases of forty-five examined, the streptococcus six times, the diplococcus intracellularis ten times, and the bacillus of Newman and Schaffer once.

This latter form much resembles the typhoid bacillus, morphologically, yet is distinct. Its discoverers claim that sterilized cultures of it cause not the slightest local disturbance; consequently the idea advanced by Grawitz and DeBary that ptomaines are unnecessary for the production of pus seems to be scarcely borne out in this instance, since this is a pyogenic agent.

While throughout these lectures and without evasion, we have taken the position that *there is, clinically, no suppuration without the action of microorganisms*, we must also insist that this expression is not intended to imply *bacteria* alone, since such other living organisms as that of actinomycosis, several of the molds, and the amœboid organism recently described by Osler, can produce it. And in the lower animals it is probable that numerous of the protozoa, as well, can provoke it. It has been stated that the injection of metallic mercury under the skin, especially of syphilitics, will produce the same result, though when the evidence to this effect is sifted, it is not found to be above criticism.

But in an inquiry of this kind it is not so important—though still most interesting—to study the rarely or unusually and uncommonly pyogenic organisms as to determine, if possible, under what circumstances the well-known pyogenic forms produce pus.

In 1861 Verneuil expressed the idea that liquids contained in the hernial sac contained toxic or irritating matters. In 1867 Nepveu found cocci in such fluid. At the Congres de Chirurgie, in 1889, Clado, of Paris, took up the question. In the contents of a sac which had contained a strangulated hernia (fatal one hour after operation), he found numerous mobile bacteria. The next day, at the section, these were found in the blood, lungs and spleen. In the strangulated knuckle there were the same microbes as in the blood, lymphatics and glands. The cultures furnished one special bacterium which, cultivated at 28° C., proved inoffensive, but cultivated between 37° and 40° became mortal within a few hours. Inoculation into the blood caused death in series. It was particularly pathogenic for guinea pigs and rabbits. In the dog it caused vomiting and loss of appetite followed by recovery. It multiplied in bodies of animals with astonishing rapidity. Clado accounts for the rapid death of some hernial cases by its penetration into the economy, taking its starting point from the surface of the intestine. Visceral congestions, so frequently observed, are the result of its localization, particularly in the lungs. Post-hernial peritonitis is held to be due to its migration through the intestinal parietes, the distention of the knuckle by gas being supposed to favor mechanically their penetration into the mucous membrane.

Bönnecken has carefully examined the fluid contained in the sac in eight cases of strangulated hernia in men, as well as in several dogs in whom it was artificially produced. In every one there were found numerous micro-organisms which proved to be identical with those ordinarily found in the intestine. A venous stasis appeared to be the pre-requisite for first the escape of fluid and then its infection. Beside the ordinary bacterium, he met with Miller's *micrococcus aerogenes*, and Escherich's *streptococcus coli brevis* and *gracilis* and *bacterium lactis aerogenes*. These bacteria were also found in the tissues and on the serous surface.

The circumstance that these same forms were found in the peritoneal cavity and in the heart's blood, means that death was caused by peritoneal sepsis and absorption of poison before pus had time to form. The author consequently holds a careful disinfection of the sac and the included loop or loops of intestine, before relieving strangulation, to be urgently indicated. (*Virchow's Archiv.*, cxx.)

Abundant corroboration of the practical value of this deduction comes from many sources. Velpeau showed that the fluid contained in the sac of an incarcerated or strangulated hernia produced an irritating effect upon the hands of the operator, and many observers since him have noticed that the escape of this fluid into the peritoneum gives rise to peritonitis without there having been any injury to it sufficient by itself to produce it. The investigations of Clado confirm those of Bonnecken; when he inoculated dogs with this fluid or its contained bacteria he produced rapid death, with symptoms of violent intoxication.

Verneuil has given to this condition the excellent name of stercoral intoxication.

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LECTURE IV.

THE RESULTS OF THE ABSORPTION OF THE PRODUCTS OF WOUND INFECTION.

Syllabus.—Surgical Fever. Intestinal or Enteric Toxæmia, and its relation to surgical cases. Sapræmia or poisoning from "Septic Suppositories." Septicæmia. Pyæmia; idiopathic or spontaneous; from causes unexposed to the external atmosphere; from old inflammatory foci. Spontaneous suppuration in previously healthy persons. Resumé of Rinne's experimental researches concerning production of sepsis.

FOR PRESENT purposes and in the light of the pathological knowledge of the day, I propose to group under five distinct headings the various septic disturbances which may result from injury or wound, which in time past have been variously regarded and classified, and which furthermore have been all summed up by the laity under the comprehensive, yet inaccurate name, blood-poisoning. These five forms are as follows:

1st. Surgical fever.
2nd. Intestinal toxæmia.
3rd. Sapræmia.
4th. Septicæmia.
5th. Pyæmia.

First. Surgical fever.—Under the term surgical fever, aseptic wound fever or fermentation fever, are included those immediate febrile disturbances which result in two or, at most, three days after an injury or a wound. This form is characterized mainly by pyrexia, with only so little nervous, emotional or digestive disturbance as seems always to accompany the same grade of pyrexia. It was called fermentation fever by Bergmann because it was supposed to be due to the fermentation of some fibrinous substance, or to be connected in some way with the fibrinous ferment. It has been shown by numerous observers that the introduction of blood into healthy animals by transfusion would produce a rise of temperature, indeed intravenous injections of clear water, or of salt solution, have the same effect, as do also injections of aseptic emulsified substances, such as water containing finely pulverized charcoal, in suspension. Bergmann further showed that such a fever may also be produced by intravenous injections of pancreatin, pepsin and trypsin. It would appear further that albuminoid substances when undergoing oxydation occasion rise of temperature, which proceeds until the products of oxydation are eliminated through the kidneys. The most probable and most satisfactory explanation of surgical fever is that it is due to the trifling disturbance attending absorption of minute products of aseptic tissue necrosis, or the oxydation or metabolism of the same. It is not always met with, and may vary in degree according to the age and condition of the subject. It speedily subsides by lysis, and has in it absolutely nothing implying sepsis, nor is it anything except a phlogenic conservative process.

Second. Intestinal toxæmia.—I give this topic a distinct caption of its own because I am very sure its importance is always under-rated by students and junior practitioners, and often by their seniors, as by writers generally. Indeed, under this term are included conditions which, perhaps, deserve to be grouped separately, though as yet we lack such accurate knowledge as shall permit a proper classification. Intestinal sepsis or *enterosepsis* has, indeed, been mentioned by Billroth, and by other writers, and yet it has been difficult to determine precisely what they meant by these terms. *Enteritis septica* is described by Gussenbauer, but it is hardly the term to apply to the condition now under consideration. Under this caption, then, I include, 1st, a condition of unusual, or at least undesirable activity in the contents of the intestinal canal, by which, whether due to common or specific forms of bacteria, the ptomaines of putrefaction are produced in such manner, or such quantity, that they are absorbed through the intestinal mucosa, and distributed over the body, by which a condition of intoxication is produced. In this form it is not meant to imply that any of these bacteria gain access to the circulation, only that a more or less profound toxæmia is produced. 2nd, a form in which the common or uncommon bacteria met with in the intestinal canal pass into and infect the living tissues of the patient, and produce local or general infection in addition to the toxæmia above described. That the first form occurs alike in surgical and medical cases I think no one will deny. That the second form is possible, if not common, is made sure by such researches as those of Karlinski. He fed animals with milk infected with staphylococcus aureus. Among forty-eight experiments he found six times general infection with swelling and reddening of the intestinal mucosa, while the fæces and the blood both showed the same cocci. Five times he found suppurative parotitis without intestinal lesions; seventeen times acute and fatal diarrhœa; eight times general infection with metastatic abscess. (He often noticed an increase of virulence after passing these cocci through these animals.) (*Prager Med. Woch..* 1860, No. 22.)

Aside from these experiments of Karlinski, there are numerous other observations all tending to show that the most common inhabitant of the alimentary canal, the *bacterium coli commune*, may be taken up by the intestinal absorbents and conveyed to at least neighboring points, where it may set up abscess with its attendant symptoms. It is extremely probable also that other intestinal organisms may take the same course. In this way, for instance, are to be explained the abscesses in the liver which accompany or follow dysentery, and in which living organisms have been described by Kartulis, by Osler and by others.

A very careful study of the pathological and infectious properties of the bacterium coli commune has been very recently published by Tavel, of Berne. (*Corres. Blatt. f. Schweizer Aerzte.* Juli, 1889, page 347). It was in 1878 that Kocher emitted the idea that suppuration of goitrous tumors was due to a secondary infection from the intestine, consecutive upon an enteritis. Tavel, studying two such cases carefully, was able to obtain pure cultures from the pus of a bacillus which produced gas, and which closely resembled bacteria of the large intestine. These he described in 1887. During the present year he had opportunity to study yet another similar case. In February there was operated upon an enormous goitrous tumor composed of two cysts; one of these was completely enucleated, the other partially so. During the operation there was a violent hæmorrhage which was checked by pressure with sponges. Some hours later there was collapse, and infusion of salt solution for the relief of the traumatic anæmia was practiced with success. A little later, on account of secondary hæmorrhage, the dressing was removed and compression with sponges again practised. The next day the drain was removed, as usual in Kocher's clinic, and was placed in jelly without developing any colony until after it had been present several weeks, when there developed a small coccus which did not liquify the gelatine. In the meantime cicatrization of the wound as complete, when there presented a hæmatoma which called for puncture. At this time two cultures were made from the blood of this cyst; one of these developed a pure culture of a short bacillus, which by accurate comparison was positively identified as the bacterium coli commune. The subsequent course of events in this case was very different from that of a mixed surgical infection. The walls of the hæmatomatous cavity became necrotic, but secreted neither serous fluid nor pus. When this cavity was scraped out later, there was removed a small fragment of sponge. Strange to say the sponge contained no bacteria, nor did the fragment removed, and the question is, did the bacteria of the large intestine reach the spot through the circulation, or did they spread there through the skin. Tavel seems to be of the opinion that in this case they reached the wound at the time when the infusion was practiced. Nevertheless, that the bacterium coli commune may become pathogenic, and, proliferating in the blood, spread to the intestine, the same author has made certain by a series of experiments, since after intra-venous injections numerous animals died, and in all their organs were found large numbers of these organisms. Even subcutaneous inoculation was enough to cause death in numerous instances. Such cases as Tavel's at least demonstrate the possibility of a rare complication of wounds, and illustrate especially the necessity of paying particular attention to the intestinal canal both before and after operations.

This second form, however, is much less common than the first, and need not long detain us at present. It is especially to the disastrous results of the detention in the alimentary canal of excrementary material to which I desire to call attention now. It unquestionably brings about a condition of pyrexia, of disturbed secretion and excretion and brain action, and of wound healing, which may at times be mistaken for sapræmia or septicæmia, which may by reasonably intelligible processes be converted into one or the other of these forms, and yet which it is necessary to sharply distinguish from them. For instance, a patient with a trifling or a serious wound passes the period when we may reasonably expect a conventional amount of surgical fever, and then, owing to inattention or ignorance, permits the bowels for some days to accumulate material which should not have been retained. As a consequence of the putrefaction of this material ptomaines or leucomaines, or other toxic substances, are formed, whose absorption is favored by their retention. That the patient is thereby poisoned is soon evidenced by mental hebetude or excitement, by pyrexia increasing in degree, by fetor of the breath, by furring of the tongue, as well as by other well-known and easily recognizable signs and symptoms. Fear of blood poisoning being aroused, the region of the wound is now examined. Unless this condition has advanced too far there will be found here little or nothing to explain the evident signs of poisoning. Should now inquiry be directed toward the condition of the bowels, most significant information will probably be gained, acting upon which a laxative enema cathartic, or both, will be administered, and with the expulsion of the poisonous material the unpleasant symptoms will speedily subside. How often has this been the experience of every practitioner and, yet, how insufficiently has he reflected upon it!

It would be a mistake, however, to suppose that only when a history of constipation is obtained can this condition of affairs result. It often happens, from causes not understood, that there takes place within the intestinal laboratory such a putrefaction as produces ptomaines which are at the same time toxic and cathartic in their action, so that the irritating material is expelled by virtue of the very poisons which it has produced ; and it furthermore often happens that the exhibition of a vigorous cathartic, for instance, one of the mercurials, will so admirably clean out the entire intestinal canal, that not merely is this entire toxic action prevented or checked when present, but that a most happy effect is exerted upon septic disturbances commencing elsewhere.

I regard this intestinal toxæmia as a subject of immense importance, further, because I am convinced that a condition which begins as a disturbance of this kind may become merged into one of the more serious or septic conditions to be mentioned soon, thereby flooding the area of the wound with organisms introduced directly from the alimentary canal, or so depressing the vitality of the patient as to permit true putrefactive or pyogenic infection from without, when this would not otherwise have occurred. In this connection it is of value to recall that particular function of the liver which has been termed its depurative action, by virtue of which it filters out from the portal circulation those elements which are harmful or toxic to the general economy. It will thus be seen that its role in preventing intestinal toxæmia is a most important one and that if it be prevented or impeded in its action the patient must suffer in proportion. The advantage then to the surgical patient of a healthy liver is simply inestimable, and the beneficial action of a vigorous cathartic administered before an operation, and, perhaps, occasionally after it, by which the function of the liver is stimulated and its canals unloaded, may be the better appreciated.

So far as differential diagnosis between this condition and those to be spoken of, is concerned, it must be based on, first, the general, and second, the local condition of the patient. If there be evidences of poisoning which can be traced to the wound, the trouble may well arise there; while on the other hand, if the wound be healthy without any evidences of lymphangitis or cellulitis, and without odor or retention of secretion, the explanation is presumably to be sought for elsewhere. Finally, in case of *doubt* the administration of a cathartic will probable settle the question. (*Vide* also the topic of stercoral intoxication at close of Lecture III.)

Third. Sapræmia.—This term was introduced by Mathews Duncan and seems to fit the case as well as any one of the numerous expressions intended to imply the condition. Such other terms as putrid fever, putrid intoxication, etc., are as expressive but not as elegant. Perhaps the best definition of the term can be conveyed by an illustration of the condition itself, and for this purpose none will serve better than that physiological operation of nature's own performance, namely, the act of parturition. By the completion of this operation there is inflicted a fresh and bleeding wound of large area, which is more or less exposed to putrefactive agencies. By the conclusion of the act and the contraction of the uterine walls there is left a comparatively small cavity which must contain a small amount of freshly coagulated blood. It is unnecessary to speak of what occurs when the puerperal state is passed without incident, but let us suppose that on the third or fourth day the patient is found with a flushed face, dry tongue, some mental disturbance and a considerable degree of pyrexia, while we are informed that the lochial discharge is altered both in appearance and in odor, the latter being now offensive. The explanation of affairs is very simple. Germs of putrefaction which were introduced by carelessness during the act of labor or afterward, have lodged in the contained blood-clot, have caused putrefactive processes, as the result of which ptomaines have been formed. We have then a condition of putrefying and poisonous blood-clot contained within a mass of tissues in which changes and absorptive processes are rapidly taking place; in other words, within a locality where absorption is highly favored. The condition being recognized an antiseptic douche is administered, and frequently repeated, by which means putrefaction is not merely checked, but abolished; and, the source of poison being removed, the natural recuperative powers of the patient enable her to recover within a few hours from the dose of poison received.

In this case we have had to deal with putrefaction occurring within a body cavity, and yet not involving the living tissues of that body. In other words just such a poisoning as might occur if we were to take rotting blood-clot and deposit it in a pouch under an animal's skin. Precisely such a condition of affairs occurs in surgical work. In an amputation stump a certain amount of bleeding has occurred, due, perhaps, to insufficient hæmostasis or to lack of proper quietude after the operation. This clot becoming first infected from a failure in antiseptic practices, begins to undergo changes in a precisely similar manner, and the patient to show signs of poisoning. If now these be recognized in time, and antiseptic irrigation with adequate drainage be established, the harm already done can be quickly undone, while the patient has suffered only a temporary toxic excitement.

In the writer's estimation it would be well to limit the term sapræmia to just so much disturbance as is included in the above illustrations, and to extend it no further. Just so soon as the putrefactive action extends from the contained clot to the containing tissues, the case should cease to be considered one of sapræmia, and should now be regarded as one of septicæmia. It is necessary then to add to the above statements only this, that a distinct form of intestinal toxæmia may become converted into one of sapræmia, simply by a continuation of the orginal condition which predisposes to the other.

Fourth. Septicæmia.—For the writer the difference between sapræmia and septicæmia is not one of character so much as of location. The idea conveyed by the term sapræmia is intended to be that of a putrid suppository, if one may introduce this illustration, from which absorption is continuously taking place; whereas in a case of septicæmia the putrefactive action is no longer confined to material enclosed by, yet strictly speaking without the tissues, but has spread from this to the tissues themselves. Pursuing our previous illustration still further, let us suppose that the recently delivered uterus has contained for some hours its putrid intra-uterine suppository of breaking down material. Presumably by the deleterious action of the poisons therein produced the vulnerability of the tissues has been so far lowered that they no longer resist the action of the micro organisms present. So soon as these have begun to attack the still living tissues, their action is, at least within certain limits, progressive; not so much by means of the circulation as by means of the continuity of tissues, the systemic poison all the while being intensified. So rapid may be this action, as it seems to be in many malignant diphtheritic cases, that the individual speedily succumbs before many evidences of abscess or local gangrene can appear. Or on the other hand providing that the toxic action be less pronounced or the patient's vitality more enduring, or providing also, which amounts to the same thing, that his tissues are more resistant locally, then abscess or local gangrene may result, the destruction of tissue being limited to the part first involved. Should this have been the uterus this favorable local destruction is less likely to occur, but should it have been in an extremity a natural separation or a mutilating operation may be the means of saving the patients life.

From what has been said, it will be seen how easily a case originally sapræmic may become merged into one of true septicæmia; but it is not intended to imply that the sapræmic condition must always preceed, since many cases begin as pronounced septicæmia from a local infection. When we have to deal with a retained and putrefying blood clot, the case is usually of the former character, but when with a direct local infection, as for example, a dissecting wound, it is usually septicæmic from the beginning.

Fifth. Pyæmia.—The distinction between septicæmia and pyæmia also is one not of toxæmia, but of the formal progression of a series of embolic disturbances, which give rise to the formation of metastatic foci and abscesses, along the lines so well laid down by Virchow. Just what it is which *determines* the formation of minute thrombi and their dislodgement and transportation first to the lungs and later to the system at large, we have not yet determined. Still, so far as can be seen, the distinction between purely local ravages such as those implied in a typical septicæmia and the dissemination over the body of hundreds or thousands of minute, infected emboli, which is comprehended in the term pyæmia, is a matter not clearly understood. It may be pure accident, or it may be something not yet clearly grasped by our apprehension; at all events it scarcely seems to be due to any pathogenic differences in the bacteria involved, for, so far as we at present can see, precisely the same organisms may produce at one time the former character of disturbance, at another the latter. Nor is the matter cleared up by a post-mortem examination of the parts primarily involved, since we are quite likely in each case to find the local veins more or less filled with clotted or semi-clotted blood, with everything favorable for its transportation to all parts of the body. It is scarcely enough to say that we have rather a phlebitis to contend with in the latter case than in the former, since that would imply that in the latter instance the walls of the veins are more easily permeable by the bacteria at fault.

It is acknowledged that in the above description of these various forms their more typical manifestations have alone been utilized. That intermediate or mixed forms are frequently met with is distinctly acknowledged by the introduction into literature of such expressions as *septico-pyæmia*, *pyo-sephthæmia*, etc. The term *kryptogenetic pyæmia*, introduced by Wagner, scarcely has any place now, inasmuch as we cannot conceive of any form of surgical sepsis which is not kryptogenetic in its etiology.

Few subjects, if any, have more deeply engaged the attention of surgical pathologists than those included under these above headings, and to attempt to summarize the literature and the views of the past, would be to lay before you a work at least no smaller in volume than the scholarly treatise of Gussenbauer. Nevertheless, with the introduction of bacteriological studies into surgical pathology, new phases of old questions have been presented and a vast amount of laborious research has been devoted to illumining them. Since Koch's masterly and path-breaking treatise on the infectious diseases, no original work has appeared upon the subject so creditable in its attacks, and so replete with experimental investigation, as that of Rinne, to which we purpose to give some attention in detail.—*Archiv. f. klin. Chir.*, Bd. 39.

The term Pyæmia was first suggested about fifty years ago by Piorry, and was used by him and others in the old humoral sense. Later the name was continued by Virchow though retained in a revised meaning. With such revised views, with the introduction by Recklinghausen of the term *embolus*, and with a recognition of the possibility of *capillary emboli*, the phenomena of metastasis became susceptible of easy explanation. That bacteria, introduced through respiratory or alimentary passages, or some open wound however small, or carried by the body juices from some local infection, are important contributing agents in this process, is a matter of much more recent development. We have learned furthermore that while it is within their province to thus provoke suppuration, deep or superficial, mild or fatal, there must be certain favorable disposition of the fluids or tissues to permit such action. We may say that their resistance is lowered; we may call it reduced vitality; we may call it vulnerability;—it matters comparatively little so long as we appreciate the fact.

While we are yet blind to all that constitutes this predisposition we may yet recognize certain conditions as predisposing to suppuration; *e.g.*, subcutaneous injuries, extravasations of blood, presence of foreign bodies, etc. We all acknowledge the existence of *loci minoris resistentiæ*, but can explain very few of them. The endeavor to account for them leads one into a very wide and yet untrodden territory.

As showing what emboli may do, take the following illustrations:

Fraenkel made a very careful study of two cases of sepsis taking its origin from the pharynx. One was a case of pericarditis and double pleurisy. The exudate at first sero-fibrinous, later contained the streptococcus pyogenes. Endeavoring to explain its occurrence in these closed cavities he maintains that organisms, aside from that of tubercle, can reach pleuritic exudate in either of the following ways:

1. When the pleuritis is of an embolic character and when the emboli are already infected.
2. When bacteria are or can be recognized in the blood.
3. When the pleurisy is the result of inflammation spreading from a neighboring infected area by continuity of tissue, and along the lymph vessels which spread to the pleura.

In his first case thus studied there were extensive diphtheritic pharyngitis and laryngitis, followed by a large retro-pharyngeal abscess, which later involved the right tonsil and then spread into the posterior mediastinum. Consequently here the infection was according to the third method mentioned above. At autopsy the same streptococcus alone was found in all the lesions.

In the second case a provisional diagnosis of endocarditis ulcerosa was made. At the autopsy there were found widespread diphtheria of larynx and pharynx, purulent infiltration of the tonsils and their neighboring tissues, myo- and endocarditis diphtheritic, hepatisation of both lungs (catarrhal pneumonia) and large white kidneys. Streptococcus pyogenes was found in the tonsils, the lungs, the diphtheritic membrane, on the inner surface of the heart and in the capillaries of the kidneys.

He compares these cases with those reported by others where the pharynx was apparently the port of entry for septic organisms. For instance, Gerhardt's case of facial erysipelas, which proceded from the tonsils, and cases of streptococcus invasion following scarlatina reported by, among others, Löffler, Heubner-Bahrdt, and Freudenberg.

Wagenmann has reported a case of puerperal fever, in which total blindness occurred within a few hours. Dissection demonstrated pyæmic foci in various organs. Multiple, extensive emboli of the vessels of each eye were found, the emboli consisting of masses of streptococci. After rapid proliferation inside the vessels these cocci escaped from their walls and were met with free in the retina, vitreous, etc. Furthermore, wherever the cocci were found was found also pus. The former were not found without the latter.

Rinne makes a clinical division of cases of suppuration and general sepsis which has much to justify it, though the minute causes may not vary correspondingly.

1. Metastatic abcesses which occur in a typical way without visible or known external injury or lesion. Spontaneous pyæmia.

2. Pyæmia and septic cases with a recognizable and causative lesion.

3. Subcutaneous suppuration at points where there had previously been inflammation; *e.g.*, abscess following *brisement force* of a joint anchylosed from a former rheumatic attack. A case to belong in this group must be absolutely free from any lesion, however slight, of any part of the surface.

I. *Idiopathic pyæmia.*—Perhaps our best illustration of so-called idiopathic pyæmia can be met with in a case of spontaneous acute infectious osteomyelitis. There is perhaps no disease of whose bacterial origin we are more certain, and we are familiar with all the microbes which have the power of producing it, yet why they select the osseous system, or rather certain parts of it, *i.e.*, usually the diaphyses of long bones, for their attack is a question which we can not yet answer satisfactorily. Or, with Rinne, let us frame this question a little more accurately: Why are the bones selected in such a case as the above, when in a general infection with equable distribution of the blood every tissue enjoys apparently equally good opportunities? Such a question misleads, however, if one takes it for granted that all parts of the body are equally liable to invasion by any given organism. Grawitz especially has shown that there is no bacterium which manifests no preference for one tissue or organ over another. Tubercle, *e.g.*, affects commonly the lungs, liver and bones, relatively seldom the testicles or ovaries, and very rarely the salivary glands or muscles. The same organ may be exempt at certain periods of life. The brain in childhood, especially the meninges, is a frequent seat of tubercular disease; in adult life rarely so, since it usually escapes in cases of acute general miliary tuberculosis. The bone marrow and synovial membrane are frequently affected in childhood, in adults they commonly escape, though in the acute miliary tuberculosis of adults the bone marrow is again a point of predilection.

Measles and leprosy affect especially the skin, gonorrhœa involves only certain mucous membranes, typhoid fever certain intestinal structures, glanders the skin and lymph-glands, and so on through the list of infectious diseases. In tuberculosis the vascular peculiarities of pia, which is especially rich in lymph vessels, or of the synovialis, may be of effect, or the more torpid circulation in the liver, but such hypotheses as these seem insufficient when we recall that whole systems, like the muscular, including the heart, escape.

It appears then to be a natural law that every disease germ has a preference, so to speak for particular tissues and organs, although of the explanation of this fact we are profoundly ignorant. Only by an overwhelming infection, or when the normal energy of the tissues and cells is altered, is this law set aside. Viewed in this light indiscriminate metastases are violations of this law.

Among all the defensive powers of the system the capability of resorption is perhaps the most important protection enjoyed by the cells and tissues comprising the organism. This power seems to be enjoyed in the highest degree by the peritoneum, which is known sometimes to tolerate and dispose of relatively large amounts of infectious material. Grawitz and Rinne have shown how many pyogenic cocci can be introduced into the peritoneal cavity without inducing peritonitis, provided only—and this is very important—the wound made in performing the experiment is properly disinfected and made to heal *per primam.* The resorptive powers of the unbroken peritoneum are therefore very great. (Vide Lect. V.)

Experiments which lead to a contrary conclusion are to be accounted for by a failure to protect the peritoneal wound. Practicing surgeons are now availing themselves of the lesson thus taught, and are closing peritoneal wounds with great caution. That the peritoneum is by no means suppuration proof thousands of autopsies have shown; on the other hand, that the healthy, uninjured peritoneum has marvellous powers of absorption of septic germs has been equally proven by hundreds of experiments. Between the two statements there is no discrepancy; it is simply a question of its disturbed or undisturbed condition.

The next most important self protection manifested by the organism is in the degree of concentration of its albuminous fluids. Pyogenic cocci can not thrive in highly albuminous liquids. Upon a mixture of equal parts of gelatine and blood clot they scarcely grow, and in a similar mixture of pus and gelatine they do not develop (Rinne). The explanation of the measure of success attained by means of the "open method" of dressing wounds is hereby furnished; the fluids which exude from the exposed wound surfaces are too rich in albumen for pyogenic or saprogenic action to occur.

As the third variety of auto-protection we must—with some misgiving—mention *phagocytosis*. A discussion of this much vexed matter would lead too far from the present inquiry; consequently, as it has so much about it that is plausible and attractive, I must simply take the ground that it is entitled to enumeration here until its occurrence has been positively disproved.

In the combination of these three defensive capabilities we find the means by which the body, by its component parts, rids itself of the offensive germs, that is when such defense is wholly successful. When successful only to some extent it is because some part, large or small, has been sacrificed to save the balance. The portion thus yielded to the enemy is now dead, and nature at once provides for its extrusion. Under circumstances included in our investigation this extrusion is brought about either by abscess or by sloughing.

Certain well known conditions conspire to prevent defensive action on the part of the tissues, particularly severe complicating general diseases, such, e.g., as typhoid. Such a disease saps the vitality from our cells, and interferes with, if it does not inhibit, their proper function.

A condition of *predisposition* is everywhere recognized and nowhere defined or explained. Still when we keep in view the varying degrees of virulence which can be demonstrated in certain bacteria artificially cultivated, we can, perhaps, ascribe more or less of the so-called predisposition of our tissues in reality to varying degree of pathogenic potentiality in the bacteria which invade them. For instance it is well known that tubercle as well as anthrax bacilli need to be passed through a living animal body at least as often as every fourth culture in order that they should preserve their virulent powers. Whether in this way their "animosity" against animals is excited, or whether their ptomaine-excreting power is increased, or whether one necessarily implies the other, is more than one can say.

Under ordinary experimental circumstances it would appear to be necessary to inject such a quantity of the common pyogenic cocci that with them should be inserted an appreciable amount of their ptomaines in order to call forth in the animal injected any sign of more than trifling disturbance. Even when the blood of a patient is swarming with these cocci the distinctive features of pyæmia (*i.e.*, metastatic abscesses) are exceptional, and the case is usually one of septicæmia. The nearly if not absolutely complete identity of acute osteomyelitis with pyæmia can be explained by the peculiarly confined limits within which their rapid growth is pent up. Again when richly lymphatic structures, as *e.g.* the lymph glands, are involved in a septic process we see how easily microbes may gain access to the blood, and how quickly the whole body may be affected. Conversely we see also how the lymph glands must act as neighboring filters for lymph vessels which are carrying away from the given lesion the absorbed infecting materials, and why they are very easily involved and often suppurate. No matter if chemical products of bacterial growth, or alkaloids isolated from putrid material, have been known to cause suppuration, they have never been known to cause metastatic abscesses. Many dogs have succumbed to doses of filtered cultures; they have died of toxæmia, showing somnolence, diarrhœa, collapse, etc., but there *never* have been found in their bodies any metastatic abscesses. All this goes to prove that pyæmia is something more than excessive ptomaine poisoning. The fulminating septic symptoms thus produced by Panum and v. Bergmann had nothing of the anatomical picture of pyæmia about them.

II. *Pyæmic and septic cases with a recognizable and causative lesion, unexposed to the atmosphere.*—A typical case of this kind would be a suppurating subcutaneous fracture, such as Volkmann has described (*Beitrage zur Chirurgie*), or a suppurating goitre. In such cases we only need to find the port of entry of the pyogenic organisms in order to explain the rest.

Rosenbach, Passet, Krause and Wyssokowitsch, among others, have shown that when the blood is laden with infectious bacterial material, it needs usually only some subcutaneous injury to constitute the *locus minoris resistentiæ*. I say usually because Rinne found that even after injecting very large doses of staphylococcus cultures into the peritoneum fractures made subsequent to the injections healed as usual, although even the injections were contined day after day. Whether in his experiments the blood of the animal injected was found to be germ-laden he does not tell us.

Rinne further details a number of experiments in which numerous and repeated injections of pure cultures into veins or tissues failed to produce any sign of suppuration, or of disturbance of union in fractured bones; and he claims—undeniably—that mere presence of bacteria is not enough, that we must seek yet further for the explanation of suppuration and sepsis in cases belonging to this group. And although it seems to make a difference what kind of animal is experimented with, and while consequently man may be more vulnerable than some other animals, yet it is quite in accordance with our experimental experience that in our clinical surgery we may find surprises of this character equally significant.

A parallel is found in the results of the experimenters (Orth, Wyssokowitsch, Prudden) who have found that an artificially injured aortic valve creates a local predisposition for the germs of malignant ulcerative endocarditis. This injury is in effect a lesion of the tunica intima, and this seems everywhere to have the same effect.

But it is undeniable that such subcutaneous injuries as those above alluded to do create vulnerable points of attack for any micro-organisms circulating in the blood, even though these latter may not always take advantage of them. When bones are broken soft tissues are usually also torn and bruised. How is it that we find the suppuration usually in the bone, rather than in the surrounding muscle? Possibly it may be that the vessels of the soft parts are more crushed than those of the bone, so that the bone wound is more likely to be flooded with bacteria than any other region. Or is the warfare of the cells more actively waged by those of the soft tissues? To my mind it is a combination of both.

Experiments failing to clear up these important problems, we may yet endeavor to discover the exact rôle played by the chemical products of bacteria, and to see if we can trace any mutual relationships between bacteria, ptomaines and wounds, by which blood poisoning resulting from infection of a point of least resistance can be explained.

The experimental work of Grawitz, de Bary, Scheuerlen and Fehleisen has demonstrated that beside the invasion of the tissues with swarms of bacteria, there is a simultaneous action of their toxic products, which either actually results by itself in production of pus or else permits their rapid growth. It it not so much a question now as to whether injections of cadaverin, as perhaps the best known of the ptomaines, can under unusual circumstances lead to pus formation. Still less is it necessary to show how such active chemical agents as turpentine or ammonia may lead to the same result by themselves, causing a toxic action, or by inhibiting the normal chemical activities of physiological fluids, or by producing gangrene of the skin and favoring bacterial infection from without, or by so preparing the soil that its vital resistance is greatly lowered.

Clinical surgery has ordinarily no such lesions to encounter as those caused by such laboratory experiments. Rinne set himself an experimental task in which he tried to ascertain the activity of such chemical poisons as take part in the inflammatory and septic process and to learn whether they alone can cause suppuration or whether they simply favor the action of bacteria. These experiments were made with:

1. Sterilized fluids in which staph. aureus and albus, and streptococci had been cultivated and then killed by heat.

2. Sterilized putrid fluids, such as that from putrefying meat, etc. These were carefully filtered and cooked, and tested before use.

3. With Brieger's cadaverin.

They were moreover conducted with a view to ascertaining whether these substances produced either inflammation or suppuration in normal, freshly injured or cicatricial tissue or around foreign bodies.

His results briefly were as follows: Injections of sterilized staphylococcus cultures and putrid fluids into healthy subcutaneous tissues, with due precautions, do not produce pus. Even inflammatory reaction was usually absent, and he never made an abscess. Subcutaneous wounds with ecchymoses did not suppurate. He inserted shreds of wool and left them a month, and still such injections made in their proximity failed of pyogenic effect. Even when these threads were soaked in such fluids the result was the same. Equally negative was the result of injections into old cicatricial tissue. Inflammatory signs were in some instances evoked, but resolution quickly followed. After injection of large quantities of sterile staphylococcus cultures abscesses whose pus (?) was free from bacteria were a few times noted, but more often resolution occurred. After introduction of equally large doses of sterile putrid fluids necrosis sometimes occurred, which would naturally be followed by bacterial invasion. Sterile abscesses following these latter were not seen.

Worsted threads soaked in these fluids, and then variously introduced and into various tissues, gave rise for the most part only to inflammatory exudate around them, which was quickly absorbed; only very exceptionally did a very mild suppuration take place about them.

Experiment with cadaverin, according to Rinne and Grawitz, may be summarized as follows:

Solutions of cadaverin, free from bacteria, subcutaneously injected, produce according to their degree of concentration and value either a caustic action, or inflammation with termination in suppuration, or inflammatory œdema with subsequent resolution.

In $2^1/_2\%$ solution—or stronger—cadaverin completely kills the bacterial culture (staph. pyog. aureus) to which it is added. Weaker solutions in proportion to their strength delay or interfere with their growth.

Still further experiments have been made with ptomaine solutions to which living bacteria have been added. For this purpose pure cultures (gelatine and agar) of the staphylococci and streptococci were mixed with distilled water, and to this was added fluid in which had been macerated putrid meat, etc. This mixture was filtered and repeatedly sterilized, and then to it were again added fresh cultures of the aforesaid bacteria. Fluids thus or similarly prepared were experimented with in varying quantities. Small animals were found for the most part to be capable of disposing of 1 cc. of such mixtures without abscess formation, though local reaction was for the most part more acute than when pure cultures alone were used. In order to differentiate still better, pure cultures were injected upon one side of the animal's body, and pure ptomaine solutions upon the other. It seemed to make very little difference how the experiments were varied. Quantities up to 2 cc. seemed innocuous, even though injected into previously bruised tissues. Just where the line could be drawn between innocent or noxious amounts seemed to depend upon the particular ptomaine, its strength in solution, the kind of animal and its condition. It is Rinne's opinion, however, that ptomaines do, as it were, prepare the soil for bacterial attack, and that under their influence pus is more easily produced. In other words *under ptomaine poisoning of a certain degree of severity suppuration is favored and spreads*; but if this degree of toxicity is diminished or increased suppuration does not take place. If this toxæmia is combined with a traumatic lesion, suppuration may be quite circumscribed on account of a very lively cell proliferation by which a zone of protection is afforded.

Although, then, these artificial conditions thus produced in animals find no counterpart in man, they teach at least that pus production is not a specific action of one bacterium, but that local œdema, suppuration, necrosis and even sloughing may be the occasional result of an irritation of a purely chemical character. The most important practical bearing of these facts experimentally elucidated is that by chemical means the normal resistance of healthy tissues may be reduced, and that the local condition, in such cases, is not so much a question as to the violence of the local lesion as of the resistance of the cells composing the tissues involved. Such a lowered resistance may be the result of local conditions, *e.g.*, frost-bite, mechanical strain etc., or very commonly of constitutional disturbances, such as struma, scurvy, gout, diabetes, syphilis, typhoid, scarlatina, diphtheria, puerperal fever, etc.

Take, for example, Lembert's and Kocher's researches concerning acute suppurative strumitis; they found it six times following after typhoid, three times after pneumonia, once after bronchitis, and once after puerperal fever, and also after acute gastro-intestinal catarrh. (*Deutsche Zeitschrift f. Chir.*, bd. x.) Five times along with the suppuration they noted putrefaction of the pus with formation of gas before opening the abscess. Furthermore they noticed that the thyroidal trouble did not begin during the general disease but as a sequel. Numerous other observers have noted the same feature in other manifestations of an analogous nature, as post-typhoidal phlegmons, etc. Thyroidal abscess is practically unknown as the result of injury alone; it results only from reduced vitality of the local tissues. For instance, thromboses, hæmorrhages, retrograde metamorphoses, in a goitre, constitute so many methods by which tissue resistance is diminished; to these may be added many constitutional conditions.

The thyroid is here taken merely as an illustrative organ; the same may be said of the bone-marrow, the liver, etc. The alimentary and respiratory passages offer open channels for infection, and after pathogenic organisms once enter the circulation they find their easiest prey in organs thus weakened.

In order to study more accurately the relations which ptomaine poisoning bears to the peculiar lowering of vital resistance that predisposes to suppuration, Rinne undertook a careful series of experiments based upon the intent to demonstrate:

a. Whether under otherwise similar conditions certain portions of the body developed differences of reaction under artificially produced toxæmias. For this purpose the peritoneum and the knee-joint were selected; the latter for the reason that invading cocci seem to be longer tolerated in the synovialis, and consequently have more time for multiplication. It was necessary further to determine

b. Whether circulatory disturbances such as hyperæmia and œdema, which could be produced by ligating veins, prepared the soil for such infectious organisms; and

c. Whether trophic disturbances, such as might be caused by division of nerve trunks, exerted any influence upon the development of bacteria. The experiments were so arranged that infection was produced as well by indirect contamination of artificially induced thrombi as by direct introduction of microbes into the veins.

The inferences which can be legitimately drawn from his experiments are as follows:

Through the absorption of putrid and infectious material open wounds which show a tendency to heal have this tendency so far changed that they permit the action of saprophytic organisms from the surrounding atmosphere. His experiments did not show that any localization or infection took place from such pyogenic cocci as were introduced into the circulation.

Consequently such irritative agents as affect open wounds, in such cases, come from without the body rather than from within. In other words the internal condition is one of lower resistability, which makes the external lesion a *locus minoris resistentiæ* so far as micro-organisms from without are concerned. But in the wounds which exhibited these phenomena, the bacteria which had been injected were never recognized in the discharges; such appeared to come only from the air.

The conspicuous part which thrombi play in both physiological processes and pathological disturbances is well known. Surgical experiences dating back to the pre-antiseptic days richly teach the disasters due to breaking down of thrombi in suppurating and putrefying wounds. Secondary hæmorrhage alone, from this disease, has been in time past the cause of a large mortality rate.

Degeneration of intra-venous clots in cases of periphlebitic phlegmons is even more frequent, and is an important part of the pyæmic process. Any experiments, therefore, which shed additional light upon the subject of the infectiousness of thrombi should be hailed with delight. Thrombi are intentionally produced at times, as after ligaturing vessels, either in their continuity or after their division; and they form as result of contusions and similar injuries, after frost-bite, etc. It is of great importance to learn how such thrombi behave toward cocci circulating in the blood, and whether they are so far attacked by the latter as to break down into pus.

To this end Rinne undertook another series of experiments by which thrombi were formed in various artificial ways, which clots he later sought to affect by pure cultures and putrid fluids introduced by various channels. Migration of pyogenic cocci into these thrombi, or into the pulmonary emboli thereby caused, was not to be detected in a single instance. Whether the animal was suffering from existing phlegmon or abscess, or whether it was so poisoned with putrid material that it died, seemed to make no difference; *thrombi* which were *not exposed to the air* were *not invaded by the pyogenic bacteria.* Hæmorrhagic infarcts did not occur in the lungs, and pulmonary emboli caused no appearances of metastatic inflammation. If infected emboli were deliberately used in the experiment in quantity then gangrene of the lungs followed; if their number was small then each tiny embolus seemed to become encapsulated by a proliferation from the intima of the vessel in which it lodged. Something similar was observed by Panum in 1862, who found that small toxic emboli were encapsulated.

Thus from Rinne's investigations it appears that neither such thrombi from ligature of veins, nor the areas immediately adjoining pulmonary emboli, nor the clots in the pulmonary arterioles resulting from emboli, nor lesions of the intima caused by deliberately injuring it, by themselves constitute in any sense points of predilection for the activity of pyogenic cocci. That is such thrombi and emboli as are protected from contact with the air do not constitute favorable soil for pyogenic bacterial invasion.

In confirmation of these statements we have others by different investigators: thus Wegner (*Experimentelles z. Lehre von Ovariotomie, Archiv. f. klin. Chir.*, xx), claims that blood effused into the peritoneum does not decompose if air be not admitted. And Mikulicz (*Archiv. f. klin. Chir.*, xxii) has declared blood clot to be a poor soil for development of coccobacteria septica. Thus from several independent sources it is made to appear that blood clot alone, without access of oxygen, offers no attractions for the bacteria of the septic state.

III. *Subcutaneous suppuration where there had previously been inflammation or some other disturbance.*—When a joint which has become anchylosed as the result of previous rheumatic synovitis or of epiphyseal ostitis, and about which there are no present signs of inflammation, undergoes *brisement force*, and then without the slightest external lesion suppurates, and when, as often happens, the pus is of the ichorous variety, we evidently have to deal with a case which belongs in a class by itself, since contamination by bacteria through the unbroken skin is excluded from the possibilities of the case.

Cases with small abrasions of the skin, with ecchymoses of the skin, or with superficial hæmatomata are not included in this class. Such cases have been reported by numerous authors (*e. g.*, Volkmann and Oberst, *Centralblatt f. Chir.*, 1885, Nos. 15 and 21; Müller, in Bruns' *Beitr. z. klin. Chir.*, iii, 2; Gussenbauer, *Deutsche Chirurgie*, Lief. 4, p. 125 *et seq.*; Köhler, *Charite-Annalen*, iii, p. 464; Rinne, *Archiv. f. klin. Chir.*, xxxix, p. 71), and one case in the writer's own experience has demonstrated to him their occasional occurrence. For their explanation two working hypotheses have been advanced: The first that some infectious material, living or inert, gains entrance into the circulation through the respiratory or digestive tracts, and thereupon finds in the spot affected a *locus minoris resistentiæ*; the other, that at that spot spores of the previously active germs have remained dormant, hibernating as it were, till some peculiar and favoring conditions could favor their reactivity.

In an address before the Philadelphia Pathological Society, in April, 1889 (*Am. Jour. Med. Sci.*, 1889), the writer alluded at some length to this latter theory as furnishing the key to certain problems in the study of acute infectious processes in bone, and towards it, as being equally explanatory of other clinical facts not relating to the osseous system, both the experiments of many investigators and the general consensus of opinion more and more point.

In the endeavor to elucidate this subject Rinne carried out further experiments as follows:

He operated on five dogs by introducing in their subcutaneous tissues worsted threads, most of which had been steeped in putrid solutions or pure cultures, or both. At the same time he introduced sterilized threads into their knee-joints. Nine or ten months later these animals, all of which survived the first procedure, were again subjected to endeavors to bring about infection by daily injecting into their abdomens active cultures of the pyogenic cocci, while they were at the same time fed with putrid meat or had subcutaneous injections of putrid fluids. At the same time mechanical injuries were inflicted on those parts of their bodies where lay the foreign bodies introduced months previously; they were contused or bruised, in the expectation that under the influence of the new infection acute abscess would be there and then produced. Astonishing amounts of putrescent and putrid material were ingested or injected.

The following results were obtained: At the points where lay the old foreign bodies, both in the tissues and the joints, in no instance was fresh inflammation discovered. At places where bones had been broken there was no suppuration. Subcutaneous peri- and intra-articular hæmorrhages were not infected, though the animal succumbed to septic infection, although a penetrating joint wound, though made with antiseptic precautions, suppurated. Artificial thrombi were not affected. Their peritoneums withstood numerous injections of large quantities of cultures of pyogenic cocci (Staph. pyog. aureus) without recognizable alteration. Even the pulmonary infarcts caused by small shot, by minute pieces of rubber, or by worsted fragments, did not evince the clear types of hæmorrhagic infarcts. The regions involved in the infarct areas still contained air. The foreign bodies were encapsulated by proliferation from the intima. Emboli produced by infected worsted seemed to cause gangrene locally in proportion to the amount of infectious material which they carried with them. A fragment, 1 ctm. long, was encapsulated without reaction like an inert foreign body, although it was saturated with infectious material.

These experimental results are consequently negative in shedding the desired light; they serve to show, however, the wonderful powers of resistance possessed by certain animals. In spite of their significance in veterinary or comparative pathology we must, nevertheless, accept the teachings of clinical experience in diseases of man, since nothing appears much more certain than that recedives of suppurative and septic trouble occur in old foci of previous disease of similar nature, or localities not far distant.

In an inquiry of this character one easily reaches a limit beyond which investigations fail to give the desired information. Some of our most characteristic cases of this class occur as sequelæ of typhoid or some other of the infectious fevers. These fevers we cannot reproduce in animals, and, consequently, we cannot imitate in the laboratory the condition which so concerns us in the sick room. Again, it seems next to impossible, some say quite so, to produce a typical form of acute infectious osteomyelitis in such animals as we use for experimental purposes. Our closest laboratory imitation of this disease in man lacks some of its essential features, and it seems to be almost absolutely impossible to produce it in any such way as that in which clinical histories imply that it appears. For instance, Rinne endeavored, upon 11 different dogs, by first poisoning them with various putrid products and then contusing their bones, to reproduce some of the well known characteristics. Not once did suppuration occur. In certain experiments of my own, in the same direction, though fewer in number, I have had the same negative result.

IV. *A fourth group* may, perhaps, be made of cases of so-called spontaneous suppuration in previously healthy persons, who have never had any suppurative nor infectious disease.

Thus Bruns (*Beitrage z. klin. Chir.*, i, 237) not long since reported two cases of subcutaneous spiral fracture of the femur which suppurated; both cases died of septicæmia. One presented peculiar features. Aside from the spirally broken femur there was a compound fracture of the tibial head, the knee being widely opened. The opened joint and the compound fracture were treated according to the best antiseptic principles throughout the course of the case, and showed not the slightest disposition to pus formation. But the subcutaneous fracture was surrounded by a quantity of pus. Not the slightest skin lesion was found about the limb.

Quite recently also Steinthal reported two observations (*Deutsche med. Woch.*, 1887, No. 21) bearing on this subject.

One was a fracture of a femur about which a large abscess developed and was opened 4 weeks later; the patient died of septic trouble and metastatic suppuration. The other case was one of old dislocation of the hip, in which efforts to reduce resulted in fracture of the neck of the femur. Five weeks later incision evacuated a quart of stinking pus with the necrotic head of the femur. The patient recovered. Steinthal thinks that in the first case infection took place through the lungs, and in the latter through the intestines, since the patient suffered from diarrhœa, which was in large measure due to such diseased teeth that he could not masticate properly. He does not seem to have thought of the possibility of infection through the decayed teeth. (Vide case on page 28 of Stimson's "Dislocations.")

In endeavoring to account for these cases we must not forget how easily slight abrasions of the skin may be overlooked, or, perhaps, healed before our examination; nor the fact that a contused and bruised, though unbroken skin, may not offer perfect protection against the penetration of germs from without. The difficulty of studying the subject is much enhanced by the rarity of such cases as those just alluded to. In the effort to elucidate it Rinne formulates a question about as follows:—Is it possible that in such cases bacteria, entering the healthy body by whatever channel they may, can segregate themselves in the subcutaneously injured tissues?

If an exact answer can be given to this query much of the mystery attending spontaneous inflammation and suppuration is cleared up.

Wyssokowitsch (*Zeit. f. Hygiene*, I.) investigating the fate of micro-organisms when injected into the blood of warm-blooded animals, demonstrated that most of them vanished in a short time, while a certain group, varying according to their variety and the quantity in which they were introduced, increased and multiplied up to the time of the animals' death. In this latter group he placed the staphylococcus aureus.

It has been further shown by Passet and others that of the pyogenic cocci these staphylococci aurei after incorporation into the body can exist—according to circumstances—in the blood and tissue juices, in an active state, for great lengths of time. They may be then eliminated, by which convalescence or recovery are established, or they may settle in some particular locality and determine suppuration, or after rapid reproduction and ptomaine formation the animal or patient may succumb to general infection, without displaying any localized pus production. It would seem as if a subcutaneous injury should act as a *locus minoris resistentiæ*, and that if any bacteria had gained access to the circulation they would have easy access to the lesion. Such would be an easy way to explain accidents like those suppurating fractures mentioned above. Rinne planned and carried out a long series of experiments well calculated to show that subcutaneous mechanical lesions either were or were not ordinarily such *loci minoris resistentiæ*. All sorts of injuries were inflicted and all sorts of irritating and infectious material were introduced or injected. For instance, a sponge as large as a hen's egg was cleaned and sterilized and then infected with twenty drops of fresh pure fluid culture of staphylococcus aureus. The abdomen of a dog was then opened, this infected sponge buried there, and the wound carefully closed. At first fever, vomiting and loss of appetite disturbed the animal, but it fully recovered in six days and remained well. Three months later at autopsy there was no evidence of peritonitis. In the omentum was a tumor, which consisted of the sponge surrounded by a fibrous capsule 1 ctm. thick. *Cultures* from the substance of the sponge *returned luxurious growth of the same staphylococcus aureus.*

Similarly endeavors to establish a focus in the kidneys, by exposing one and drawing through it a piece of wool and leaving it there, closing the wound antiseptically and then injecting elsewhere pyogenic cultures or putrid material, were equally unsuccessful.

Apparently, then, this question as to the localization of bacterial activity at the site of mechanical lesions must receive a negative answer. One is astonished to find how little evidence of local action appears on section of the tissues at the point in question. After scores of such apparently crucial experiments it is noted that nothing was found here. Intentional lesions quickly healed, foreign bodies encapsulated, hæmorrhages resorbed, and not once was local suppuration observed. The clinical experiences of every surgeon afford many parallel instances.

Rinne, more than any one else, has called our attention to this aspect of the subject, that the pathological importance of the pyogenic cocci has, perhaps, been greatly overestimated in this respect, *viz.*, not merely whether they *can* produce pus, but whether they invariably *do* or *must.* Herein lies a vast difference. After their discovery some were inclined to grant them a specificity akin to that of the erysipelas germ. But of late these views have somewhat modified. Rosenbach and still more Passet, showed how frequently the staph. pyog. alb. and aureus., less uniformly the strept. pyog., produce abscess formation. But we see, sometimes, reactionless absorbtion follow, and sometimes fatal blood poisoning, after injecting the same organisms. The researches of Grawitz and de Barry concerning purulent inflammation were enough to limit the specificity of these cocci. Then Scheurlen, Fehleisen, Bumm and B. Fraenkel confirmed their conclusions, in the main, and showed that the role of pyogenic cocci in causing progressive suppuration is really a limited one. It has been made necessary for us to seek further for contributing causes of suppuration.

In 1887 (*Tageblt. der Natur-forsch. Versamml. zu Wiesbaden*, 1887, p. 157) Rinne formulated the following conclusions:

1. Animal bodies have the capability of eliminating pyogenic cocci, when these, after introduction into the tissues, are protected from direct contact with oxygen.

2. A migration of cocci in a subcutaneous injury, or in a sterile abscess produced by injection of sterile chemicals, does not occur, nor does it, after injection into the circulation or the peritoneum.

3. Even after direct injection into fresh cutaneous wounds, into young or old cicatricial tissue, or around foreign bodies, there is no suppuration.

4. It, therefore, follows that tissue lesions which determine inflammatory reactions, at least, do not predispose for metastatic suppurations; nor do thrombi.

5. But it is comparatively easy to convert such lesions into *loci minoris resistentiæ* by introduction therein of the chemical products of bacteria. Such a *locus* is any tissue whose normal resistance is lowered by any chemical or mechanical lesion; but so far as acute inflammations are concerned they do not constitute—of necessity—such *loci* by any means.

Hence arises an inquiry of immense importance.

What sort of injury to a tissue is necessary in order to so lower its power of resistance as to predispose it to bacterial invasion?

From the failure of experiments already sufficiently indicated it becomes evident that this inquiry needed to be directed along other lines. Still working at the subject Rinne adopted a somewhat different plan of action, and endeavored now to introduce the bacterial material directly into the injured area after inflicting a lesion. *A priori* it would seem much easier to thus convert such an area into a suppurative focus. These experiments comprised such procedures as the following:

Subcutaneous sections of tissue; immediate injection of bacteria into the section thus made.

Subcutaneous introduction of glass balls filled with bacterial cultures; time for healing or encapsulation given; then, the balls being broken, liberation of their contents; still later injection of cocci into the injured tissue.

Subcutaneous injections of infected fluids.

Injections of cocci into old scars.

Encapsulation of shreds of wool which had been saturated with pyogenic cocci; these were tried in the joints, peritoneum, subcutaneous tissue, etc.

These last were undertaken especially with a view to determine whether mechanical injuries to tissues with exclusion of oxygen predispose to bacterial proliferation; and only in this last series was suppuration produced at all, and here only when the wool threads were infected. Even then the suppuration was not progressive in character and the cocci seemed to starve very quickly.

It appears then that mechanical lesions, *in loco*, do not predispose to bacterial, *i. e.*, pyogenic, activity, in other words to phlegmonous processes, *provided* that the locality is protected from access of air, that is of oxygen. In subcutaneous injuries absorption takes place too rapidly for the cocci to have time to form ptomaines, to disturb the tissues or to proliferate. Even in cicatricial tissue and in the neighborhood of scars, there is no *locus minoris resistentiæ;* resorption even here is scarcely hindered. The quicker the resorption the less noxious the bacteria. Rapid absorption and lively tissue-cell proliferation are really both protective in high degree; the "battle of the cells" being the defensive feature of the latter. Therefore lesions which cause an inflammatory reaction by no means predispose to metastatic suppuration.

Mechanical disturbance can also afford to cocci previously present in the tissues opportunity to set up a suppuration, by gaining access to some foreign body penetrating the tissues, and there producing ptomaines by whose help the process is established. That such a process is purely local is brought about by the factors just mentioned above.

In further elucidation of the precise part played by purely chemical agencies—by ptomaines like cadaverin, or by caustics like ammonia or croton oil—which without bacterial help can provoke a muco-fibrinous exudate, Rinne carried out yet another series of experiments intended to show whether there could take place an emigration of microbes from other parts of the body into an inflammatory focus caused by such chemicals. After producing such foci in various animals (dogs and rabbits) pure cultures of pyogenic cocci were injected:

a. Subcutaneously at distant points.
b. In the abdomen.
c. In the circulation.

In no instance could these cocci be recognized at the point in discussion; not even when extensive phlegmon was produced at the point of bacterial infection.

The order of the lesions was then reversed, without altering the result.

When an actual necrosis of tissue was produced then sometimes a penetration of ordinary bacteria from the air was observed, but nothing more.

Sometimes along with the croton oil, cadaverin, etc., the pyogenic cocci were injected at the same time, and then acute phlegmon was often produced, along with partial skin gangrene, and then the above cocci would be found along with other forms. But more often the result was a severe caustic action with extended necrosis and then mummification.

From these it appears that such chemicals of themselves produce no spot of least resistance for pyogenic cocci; and further that ammonia or cadaverin, when sterilized, may

1. In a certain concentration produce abscesses with sterile pus (puruloid).

2. Or prepare the soil for bacteria which are injected with them.

3. Or by destroying the overlying skin permit access of any of the organisms from the air; but that *they cannot* open the pathway for bacteria from the blood of the same individual; the explanation for which is probably to be found in a very lively cell proliferation.

Accordingly while it thus appears that chemically produced lesions do not predispose to bacterial activity, it further is seen that just as little also do the subcutaneous inflammations thus produced favor metastatic suppuration or become *loci minoris resistentiæ*.

Finally Rinne propounds this query: Wherein lies the key to the comprehension of those cases where abscess occurs without our being able to recognize any disease or point of infection?

Everything points to the impossibility of a purely spontaneous suppuration, as well as to the complex character of various contributing factors. And first of all the histories elicited are seldom of value enough to shed real light, and examinations of patients are seldom scrutinizing enough.

Then it must be remembered that the lesion permitting entrance of bacteria may be healed before the abscess comes under observation; *e. g.*, pelvic abscesses or endocarditis puerperalis ulcerosa some time after puerperal fever, etc. Thus Grawitz reported to Rinne a case where a purulent basilar meningitis was traced along the second branch of the trifacial nerve, and found to have its origin in a furuncle just over the infra-orbital foramen, which had almost healed.

Moreover the primary lesion may present no clinical signs and so be passed unnoticed; *e. g.*, the abscesses or meningitis known to follow pneumonia. Probably so-called idiopathic peritonitis or pleuritis, like the so-called rheumatic, come under this category.

Acute infectious osteomyelitis was formerly regarded as a purely idiopathic disease; now we know that it is a staphylococcus infection, but sometimes find it difficult to trace the path of infection. It may follow typhus, scarlatina and diphtheria, or perityphlitic or pelvic abscesses, for instance, which may have been long past; or it may follow some external furuncle or phlegmon.

But it often happens that the septic or suppurative process has reached its height when the case first comes under accurate observation and that the lapse of time has obliterated in one way or another those evidences which might lead to a more speedy and accurate recognition of the prime causes for which we seek. Previous "feverish states" offer a much more plausible explanation for many cases of so-called spontaneous suppuration than do the majority of histories of injury.

LECTURE V.

PERITONITIS.—TESTS FOR ANTISEPTICS.

SYLLABUS.—*Peritonitis.* The peritoneum and its capability of absorption; rapidity of same. Influence of any ascitic fluid present. Effect of injections of various pyogenic organisms and in varying quantities. I fection of peritoneal wounds. Forms of peritonitis. Conditions under which infection takes place. Improbability of a pure type of gonorrhœal peritonitis. Distinction between septic and putrid forms of peritoneal inflammation.

Testing antiseptics. Method of testing the relative antiseptic value of a chemical substance with various pathogenic organisms. By the hanging drop. With spore-threads. Determination of necessary length of exposure. Results with solid culture media. Estimate of its absolute as well as its relative toxicity.

Application of these methods to an estimation of the new drug *Pyoktanin.* Disappointment experienced here as with all other drugs of its class.

OUR views concerning the susceptibility of the peritoneum and its intolerance of insult have undergone wide changes within the past few years; indeed it would almost seem to be more tolerant than other serous cavities or ordinary subcutaneous tissues. The explanation of this condition is to be found in the character of this membrane, and the conditions which obtain when pyogenic organisms are therein introduced; and first of all comes into play its wonderful capability of absorption, by which micro-organisms are deprived of their necessary nutrient fluid, along with which, as it returns to the vessels, it is quite possible they may pass into circulation to be there destroyed. For instance, Wegner introduced 200 cc. of warm serum into the peritoneal cavity of a rabbit, and an hour later bled the animal to death; the amount of fluid then present in the same cavity was only 66 cc. showing that 134 cc. had been absorbed within an hour. When fluid of lower specific gravity than blood serum is introduced, it seems to lead at first to a transudation from the blood. It is very different with a fresh wound, since here we have not an active absorbing surface, but rather the contrary. Wegner further showed that a great variety of fluids free from bacteria, such as water, urine, bile and blood may be introduced in the same way without bad results. So even with large quantities of unfiltered air. If too large a quantity of fluid capable of putrefaction be introduced at the same time with unfiltered air then there is rapid decomposition. Thus if 50 cc. of such fluid are introduced into the abdomen of a rabbit, of which only a part can be rapidly taken up, the rest furnishes a suitable medium for the growth of the organisms present in the unfiltered air which has been injected, inasmuch as such air contains ordinarily saprophytic but not pyogenic organisms. Wegner more often produced septic intoxication than true septic peritonitis.

Reichel has quite recently published an essay containing a mass of clinical reports, in which he seeks to discover what particular conditions favor the occurence of peritonitis. A series of experiments in which he injected pus with gelatine into the peritoneal cavity confirm the statement of Wegner and of Grawitz that the peritoneum is capable of absorbing a certain amount of pyogenic organisms, but that injections of relatively too large amounts are fatal. He made a number of experiments by excising a small area of peritoneum and rubbing into its denuded surface the organisms with which he was experimenting. Four out of five animals withstood this inoculation, although Grawitz did not meet with the same success in similar experiments. The results gathered from a arge number of abdominal sections in human beings agree pretty well with his experimental results. In complicated ovariotomies the peritoneum equally easily reabsorbs these foreign organisms. Ascites, which frequently occurs, offers a fine culture fluid for the growth of bacteria, and increases the danger of peritonitis. Separation of adhesions favors inflammation just as in the experiments above detailed, and for the same reason. A recent or fresh attack in infectious peritonitis does not seem to increase the danger of septic inflammation. (*Deutsche Zeit. f. Chir.*, xxx, 1 and 2).

Predoehl has investigated fourteen cases of suppurative peritonitis. The streptococci were found most commonly.

Fraenkel has also assigned the predominating role in peritonitis to the streptococci, finding them in two-thirds of all cases, especially in the more rapid forms. Only in the more slow cases did other forms appear, which proceeded probably from the intestine, and seemed sometimes to destroy the streptococci or at least antagonize their action. Fraenkel cultivated the streptococcus pyogenes from this source, and with it produced a typical erysipelas on the ear of a rabbit; also a typical peritonitis and panophthalmitis after injecting it respectively into the peritoneum and the eye.

Pawlowski undertook a series of experiments to corroborate the statements of Grawitz, who injected large quantities of staphylococcus aureus into the peritoneal cavity, without producing peritonitis. He had already shown that after the injection of such irritating substances as croton oil, an inflammation of a sero-hæmorrhagic character, but not septic, was produced. He began this latter series with relatively large quantities, which he gradually reduced, and found that only small quantities were absorbed without injury. With the bacillus pyocyaneus he produced for the most part only a fibrinous hæmorrhagic inflammation, which several days later became purulent. He also endeavored to ascertain just what element of the intestinal contents produces perforation peritonitis. He showed that filtrated intestinal contents free from bacteria are not pathogenic. Evidently, therefore, bacteria are the agents, and he isolated a short, rapidly growing bacillus, the injection of which into the peritoneum produced suppuration for a time. He also showed that given quantities of staphylococci which by themselves were incapable of causing inflammation, could, nevertheless, do so if croton oil were introduced at the same time. (*Virchow's Arch.*, 117).

In opposition to Pawlowski, Waterhouse, working under the direction of Orth, came to results which agree for the most part with those of Grawitz. He was able to inject much larger quantities of staphylococci into the peritoneum, it making no difference whether they were injected through a canula, or after incision into the peritoneum with the endeavor not to injure the intestine. He seems to have demonstrated that peritonitis occurs only when absorption is interfered with. He found also that the simultaneous introduction of blood, or strong meat broths, or ammoniacal urine or turpentine, along with the introduction of pus is always dangerous So far as the infection of peritoneal wounds is concerned, it appears from his experiments that a well sutured wound does not favor growth of organisms, but that large defects in the abdominal wall, or the mesentery, prove favorable fields for the growth of bacteria. Previous disease of the peritoneum, such as ascites, seems to favor peritonitis. He found that after injecting staphylococci several hours after an artificial obstruction, which latter of itself would be harmless, purulent inflammation supervened. Especially noteworthy were his results when, after producing such intestinal obstructions, he injected the cocci, not into the peritoneal cavity, but into the veins, or into the bones, muscles, or other tissues. It appears therefrom that the microbes thus brought into contact with the intestinal lesion do not perforate intestinal walls as long as they are not necrotic. (*Virchow's Arch.*, 1.19).

At the sixty-second Congress of German Naturalists, Orth detailed some of his experiments in the production of peritonitis. Alluding to the wonderful resistance which the peritoneums of animals have shown after injections of putrid substances, etc., he claimed that if the peritoneum be injected with the same material in less absorbable shape the result is different. Such a condition is obtained when pure gelatine and agar cultures of pyogenic organisms are used, or fifteen to twenty centimeters of freshly injected blood, so that some remnant of the injection can still be found three days later. He thinks that large amounts of pure blood clot alone are sufficient to set up peritonitis, probably not alone from bacteria but from some fibrin ferment.

Previous visceral lesions favor the activity of these organisms. In ascitic animals 1 cm. of staphylococcus fluid will cause fatal results in three to four days. In the same way excision of a piece of peritoneum, or irritating a small area with turpentine, lower its resistance greatly. Numerous experiments were made to estimate the effect of vascular disturbances. Loops of intestine were strangulated for various times. It was found that a ligature of the loop for four to six hours, by itself, did no harm, but if this were followed by injection of the above fluid peritonitis quickly ended the animal's life. Even when the strangulation lasted but two to four hours, the injection of four drops of fluid into the vein of an ear caused death in twenty-four hours. The streptococci appeared a little more slow in their action than the staphylococci.

If after temporary artificial strangulation a fracture be subcutaneously made, and the injection made into the fracture wound, the result is the same. In other words, by indirect or direct introduction of pyogenic organisms peritonits can be set up and rapidly prove fatal *providing* the local disposition be present.

Grawitz, in a careful study concerning the origin of peritonitis, has formulated the following dictum.

Pyogenic organisms mixed with absorbable amounts of indifferent fluid and injected into the normal peritoneal cavity produce peritonitis only when:

1. Introduced in excessive amount.

2. When at the same time some substance acts to produce necrosis of the tissue and thereby to prepare the way for penetration of the cocci into the deeper layers of the serous membrane.

3. When especially some wound of the abdominal wall favors localization of infection. (*Charite Annalen.*, 1886).

Pawlowski, in his researches elsewhere alluded to, had some curious results bearing on the topic now under consideration. He found that injections of fresh normal fæces gave rise to fatal fibrino-purulent peritonitis, which he considered to be produced by a particular bacillus which he termed *bacillus peritonitis ex intestinis cuniculi.*

He agrees with observers who claim that the pyogenic cocci all thrive with the greatest activity when they find in the peritoneal cavity any dead or dying tissue or cells.

He distinguishes two forms of peritonitis:

1. That produced by chemical agencies such as croton oil and trypsin, of hæmorrhagic form.

2. That produced by infection.

a. Peritonitis mykotica, of violent severity, without peculiar macroscopic features, showing microscopically exuberant proliferation of the micro-organisms on the serous surfaces.

b. Less violent type, beginning as a hæmorrhagic form.

c. Fibrino-purulent form, representing the mildest infectious variety; usually the commencement of the ordinary purulent peritonitis.

In general, Bumm makes the following different classification of forms of peritonitis, yet one which is certainly accurately founded.

I. Aseptic, usually local, sometimes generalized. It progresses to fibrinous exudate and possible adhesions. In this form there is no bacterial invasion.

II. Septic.

a. Streptococcus and staphylococcus peritonitis. Usually puerperal.

b. Putrid peritonitis. Usually post-operative or perforative. Is a mixed infection. (*Vide* Lect. X.).

The former happens most often after parturition, begins with a chill, and is accompanied throughout by high fever. On section is found thin, purulent, odorless exudate, or if late this may be thick and creamy; this exudate early in the disease is very infectious, but loses in virulent intensity as the disease progresses. As the streptococcus belongs to the facultative aerobic organisms and loses its virulence by exposure to the air, we may find here the explanation of the fact that the exudate is more infectious than the cultures of the germ. The path of infection from the genitals to the peritoneum is by no means always clear, since sometimes the tubes are quite free from the organism.

The putrid peritonitis occurs most commonly after operations; it begins without chill, with fever, which gradually runs higher, and is characterized by a putrid, ill-smelling exudate. This is slightly, if at all infectious, and contains a mixture of several organisms, many of which at least are in no wise pathogenic. This disease is the result of putrefactive organisms, which extend at the time of the operation, and quickly work their evil effects. The febrile symptoms are mainly due to ptomaines. The disease is spread locally by movements of the bowels, peristalsis. Other forms of mixed infection from perforation, etc., can hardly be classified.

III. Specific. Tubercular; Gonorrhœal (?). This last form is as yet problematical. (*Münch. med. Wochenschrift*. 1889, No. 42).

Bumm further questions the possibility of a pure type of gonorrhœal peritonitis. Pure gonorrhœal pus which escapes into the peritoneum from an infected tube sack, acts, he says, like an aseptic foreign body, and becomes encapsulated. If the contents of the tube present a mixed infection then the result may be very different.

Pernice experimented extensively to help settle this operation. He found that various chemicals like concentrated acids, phenol, strong corrosive sublimate solutions, etc., injected into the abdomen of guinea-pigs and rabbits, produced undoubted peritonitis with necrosis and perforation. But the character of the exudate was always serous or sero-fibrous, never purulent. (*Rivista Inter. di med. e. Chir.*, 1887).

Pawlowski made over a hundred quite similar experiments. Croton oil and trypsin in dogs and rabbits produced acute hæmorrhagic but not purulent peritonitis. Non-pathogenic organisms were introduced in large numbers; they produced no inflammation, even when introduced with small doses of irritating chemicals. Quite otherwise, with cultures of the pyogenic microbes; the staphylococcus pyogenes aureus produced frequently fatal purulent peritonitis; indeed he had much more pronounced results with these cocci than some others have had.

The ordinary septic peritonitis following confinement is a streptococcus infection Whether the cocci work along through the vaginal and uterine surfaces and through the tubes to the peritoneum, or whether they pass by the lymphatic vessels directly to the serous covering of the uterus, has not yet been definitely settled; if indeed they do not take either course according to circumstances. In two cases of this nature, however, Bumm has found the tubes completely free of bacteria.

In the most rapidly fatal cases one finds in the peritoneal cavity a thin, flaky, yellowish fluid, which if removed by aspiration immediately after death has no odor. It contains fibrin flakes, endothelial and pus cells, and streptococci. These latter are found as well in the genital tract, in the blood and most of the internal organs. This fluid is extremely infectious. A fraction of a drop injected into the abdomen of a rabbit sets up a violent commotion which is fatal in twenty-four hours. Injected in the tissues in trifling amount and well diluted it sets up an acute phlegmon which is rapidly fatal.

In the slower forms of puerperal streptococcus-peritonitis the peritoneal exudate is more purulent in appearance, but less virulent in its properties. Of this it takes from a few drops to two grammes to set up a fatal peritonitis in a rabbit.

So also the reaction on subcutaneous inoculation is less violent. It appears, as Bumm says, as if the virulence of the material is the more diminished the longer it is exposed to the action of living cells.

Experiments made with this exudate from fresh cases give constant results; it seems however that experiments made with pure cultures of the same organisms are followed by most uncertain consequences. It is hence abundantly proved that by cultivation these organisms loose their virulence, a fact which we know as well of the bacilli of anthrax and tubercle. Widal has referred this peculiar alteration of malignity to the fact that these cocci when at their best are ærobic, and that when cultivated in a hydrogen atmosphere they retain their infectiousness. The fact well known to laboratory workers that streptococci grow better along the needle streak than on the surface also bears out this view.

The course of an ordinary traumatic (post-operative) peritonitis, like the findings, is somewhat different. The dirty looking, sometimes badly smelling, peritoneal exudate contains now not any specific organism, but shows a mixed infection, cocci and bacilli being often found together. By plate cultures several different forms can be isolated. Intra-abdominal injections of such cultures, in rabbits, usually give no results. Only the original peritoneal exudate, and this often in considerable quantities, seems not to be infectious.

Between these two varieties of peritoneal inflammation there are thus seen to be differences not merely clinical; and Bumm, as shown above, has proposed to call the former the *septic*, the latter the *putrid*. His explanation is about as follows: No one who has done bacteriological work but knows full well that no laparotomy can be done without exposure to germs and their contact with the parts exposed. Aseptic operating comprises, virtually, exclusion of the majority of organisms and trusting to the resistance of the tissues to dispose of those not excluded. Ordinarily such microbes as enter the abdomen are killed by the cells or fluids in which they lodge. But when the peritoneum is too severely attacked, or is already weakened in resistance, then surroundings are made favorable for such germs as have entered, and the process if once begun can scarcely be checked. By peristaltic action infection is spread, and by the peculiar capability of absorption which the peritoneum possesses an enormous number of organisms enter the blood, so that patients soon succumb to putrid intoxication.

Between the septic and putrid varieties we have these distinctions:

In the former we have pus instead of ichor, and acute onset with chill and high temperature instead of a more deliberately and gradually febrile clinical picture.

As a result of these, and hundreds of similar experiments, we have learned that to produce suppurative peritonitis it is necessary either to introduce the cocci in such numbers along with their products, that a part of the peritoneum be so affected as not to exercise its proper function; or they must be introduced into an already unhealthy peritoneum, or there must be present too large a quantity of fluid to be quickly absorbed; or finally there must be present some material such as blood-clot, or dying or dead tissue, in which they can develop. (Cheyne) As Cheyne has shown, suppurative peritonitis occurs with the greatest certainty when there is a wound in the abdominal wall in which infection can occur, and from which, as a center, organisms are constantly given off into the cavity within. This is still more certain to occur if the wound be an unhealthy one. For example in rupture of a healthy bowel, if the extravasated contents are thoroughly removed and the wound early approximated, recovery commonly occurs. But in perforation after typhoid the bowel-wall is unhealthy and forms a nidus in which organisms may grow and the only prospect of success is by resection, that is removal of the unhealthy tissue.

E. Frankel has called attention to the clinical fact that the more rapid the case of peritonitis the more likely we are to find pure cultures of the streptococcus in the pus. (This can hardly apply to a perforative form of the disease.) He also shows how hard it is to always recognize streptococci on gelatine cultures alone and at ordinary temperatures, and how much more accurately this may be done with glycerine-agar media at blood temperature; and he ascribes, and with propriety, some of the negative or contradictory findings of previous observers to lack of this precaution. He also regards this streptococcus (pyogenes) as identical with that of erysipelas; and he has produced this latter disease by inoculating animals with pure cultures taken from the abdominal cavities of animals with peritonitis. With the same organisms injected into the eye he has produced, moreover, panophthalmitis, and when injected into the cellular tissue purulent infiltration.

Of the many non-specific organisms often met with along with the streptococcus, most possess the property of curdling milk and of decomposing albumen, and this latter property certainly works no benefit for the patient. Many of them produce ptomaines which have highly toxic properties. Boiled cultures of these organisms are still highly toxic, which is not true of streptococcus.

Fraenkel can hardly agree with Bumm in his differentiation between *septic* and *putrid* peritonitis, but he finds that the pure streptococcus forms give at least an odorless exudate.

He further describes a form of peritonitis determined by inorganic chemical agencies, and alludes to the frequency with which gynæcologists use tincture of iodine and iron salts. These substances, even when absolutely sterile, have the power of provoking a sero-fibrinous but not purulent inflammatory exudate, which is absolutely free from organisms and odorless. If the animal or patient live long enough this may be invaded by organisms from the intestinal canal. (*Münchener med. Woch.*, 1890, No. 2, p. 23).

THE TESTING OF ANTISEPTICS.

For the purpose of testing an antiseptic it is not enough to mix it in certain definite proportions with various nutrient media, and then endeavor to ascertain whether this or that organism will grow therein. Even if it will thus grow we have still very much to determine as to matters to be commented upon later; whereas, if it will not grow upon one or two trials it might be assigned an altogether false position.

There is systematically carried out in the laboratory of the Hygenic Institute in Berlin a method which, though long and somewhat tedious, leaves virtually nothing to be desired in determining the exact bactericidal properties and toxic effects of a given agent. It is practically a method laid down by the great master Koch, and carried out and taught by his assistants, to whom, especially to Dr. Behring, I am indebted for an acquaintance with it. It is briefly as follows: A soluble antiseptic must be dissolved in solutions of known strength; an insoluble material can hardly be properly tested. We begin, therefore, with a standard solution of the substance to be tested, and this should be of the strength of, say, 1 to 1,000. It is now convenient, knowing the dropping glass or the pipette with which we are to work, to ascertain now many drops, as they fall from its point, will constitute 1 cc. Let us suppose for illustration that this number is 80; obviously then, one drop of this standard solution contains $^1/_{80,000}$ of a gram of the substance to be tested. Two drops equal $^1/_{40000}$. four drops equal $^1/_{20000}$, and forty drops then equal $^1/_{2000}$. We experiment first with bouillon duly sterilized, and in sterilized tubes. It is best also to select three typical pathogenic organisms with which we shall conduct three preliminary series of experiments.

First, anthrax, which is the most resistant and tolerant of all of the common forms; and second and third, the staphylococcus aureus and the streptococcus pyogenes, which are representative species of generic groups that give surgeons the greatest trouble. Now 4 cc. of sterilized bouillon are placed in a tube and inoculted with a fresh, pure culture of anthrax. After the tube is thoroughly shaken, a small drop of the infected bouillon is removed with a fine platinum loop, placed upon a clean cover-glass, and this is inverted over a hollow slide, and sealed with vaseline; in other words, this is a pure culture of anthrax in a hanging drop, and is used for control. To the same tube of bouillon is next added one drop of the standard solution above referred to. One drop mixed with 4cc. now gives to the solution a strength of $^1/_{320000}$. This is shaken and a drop of this placed upon another cover-glass. A second drop is now added to the same tube, which so far strengthens the solution as to give it now a strength of $^1/_{160,000}$; after making a culture of this strength, two drops more are added, thus making it $^1/_{80000}$. The next dilution is made with four drops more, which, with the four previously added, make eight drops in all, or a strength of $^1/_{40000}$. Next, eight drops more are added, giving it a strength of $^1/_{20000}$, and next sixteen more, which with the previous sixteen, make thirty-two drops now added to the solution, and giving it a strength of $^1/_{10000}$. This process is carried out as far as we choose to conduct it, making a fresh hanging drop culture with each fresh addition of standard solution. Each slide is carefully marked with the character of the culture and the strength of the solution, and all are the placed in a cage or suitable holder, which is then placed in the thermostat where it is kept at blood heat; after twenty-four hours the slides are removed and each one carefully examined under an immersion lens. A table is then constructed showing in just what strengths of solution bacteria are found after this interval, where they begin to fail, and where they are not found. The slides are then restored to the oven and the same observations are reported at the end of the second and of the third day. The results thus obtained give us our first working data with the organism in question.

In the experiments which we are supposing, the same investigations must be made with the other two forms of bacteria above alluded to, since it will be found that a solution strong enough to kill staphylococci will by no means necessarily destroy the anthrax bacilli.

Conversely, however, we may hold that anything which will destory anthrax bacilli will almost certainly kill all other pathogenic bacteria.

Next, we introduce a series of cultures made with the so-called spore threads. These consist of ordinary linen or cotton threads which have been sterilized by heat, and which are then left for a few hours in pure bouillon or fluid cultures of the above organisms; they are then removed and dried in a safe place. With organisms which produce spores these threads become impregnated with the same, and the latter will preserve their vitality for months or even years. If, now, small particles of these threads be clipped off with sterilized scissors, and a little particle immersed in our hanging drop, there will develop there the typical organism just as under other favorable circumstances. These spore threads are used in much the same way, as above detailed; a control culture is first made, or better two of them, by placing one of these particles in a hanging drop of pure bouillon. To 4 cc. of this same bouillon are now added, drop by drop as before, given amounts of the standard solution; with the addition of each proportion a hanging drop culture being made, by inserting a particle of spore thread.

By means of the first series of experiments just detailed, we can narrow down within certain limits the proportions between which we must further work, and our experiments are thus made less discursive. These spore thread cultures are placed in the thermostat as before, and observations are made at the end of the first, the second and the third day, and the results tabulated again. This method is simple, and has much in it to attract and commend itself. It is, however, open to serious error, inasmuch as the various antiseptic solutions exert different effects upon the material of the thread or are themselves altered by it. For instance, if it is with aniline dyes that we are experimenting, the vegetable fibres take up a certain amount of coloring matter, thereby depriving the solution of so much, and vitiating our calculations. If it is with such substances as mercuric chloride, zinc chloride or silver nitrate that we are working, they also undergo mutual reactions with the same disturbance of relative strengths. So that before these tests can be considered thoroughly reliable, we must determine what these mutual reactions are. There is, further, a most important practical deduction from the above statements, since for wound dressings we depend upon vegetable material, usually cotton, which is saturated or impregnated with antiseptic solutions of various strengths. It will be seen, therefore, that it does not follow that by the time these dressings are acted upon by wound discharges, the proportion of antiseptic which they contain will be the same as at first prepared; in other words, a so-called antiseptic dressing may not be nearly as much of a protection as it would appear to be.

After determining the value of an antiseptic by the hanging drop experiments, it is necessary to determine its activity in the direction of the length of exposure necessary for the destruction of bacteria by solutions which have a sufficient strength, as determined above, to produce a bactericidal effect. For instance, in a strength of $^1/_{3000}$ a given organism does not grow in the hanging drop after 24 to 72 hours. If this has been determined, we must next make clear how long it takes a solution of this strength to kill this same organism. Suppose that we are working with a given antiseptic designated by X, and with anthrax.

Bouillon is impregnated with this X in a proportion of one to three thousand, it is then inoculated with a pure, fresh culture of anthrax, and carefully shaken. At stated intervals one drop is taken from this tube and planted in another of pure bouillon; these tubes are then placed in a thermostat and, after 24 hours' exposure there, the results as to growth or no growth are carefully noted. The intervals alluded are purely arbitrary, but are as follows: After five minutes, after two hours, and after twenty-four hours. The first period of five minutes is selected as representing such exposure as the conventional irrigation of a wound would offer; and the second and third are purely matters of convenience. These experiments should be repeated, only using blood-serum instead of bouillon. Such experiments have the definite object of demonstrating whether the given antiseptic, X, is of value when used as irrigating fluids are usually used in surgery; and they must be repeated with the staphylococcus and the streptococcus. Then bouillon cultures made like those just referred to should be mixed with X in the same proportion, and after the same intervals of time should be injected into animals, and results noted.

Furthermore, it is necessary to determine whether after a given time, say five minutes, all the organisms in a given tube are killed, or only the larger proportion. For these purposes take 5 cc. of pure bouillon in a tube, inoculate it with anthrax, shake thoroughly, remove 0.1 cc. with a sterilized pipette, add this to 5 cc. of gelatine, and make a plate culture in which after twenty-four hours the colonies are to be counted. Into the same tube of bouillon put X in the proportion of 1 to 3,000, and after five minutes again remove 0.1 cc. with the pipette, add this to 5 cc. of gelatine, make another plate culture, and so again after two hours and after twenty-four hours. After one day's exposure of these plates, which are supposed to have been kept at the same temperature with the same surroundings, either in a room or in a thermostat where the temperature is somewhat low, a count of each plate is made. The number of colonies in the first plate, multiplied by 50 (=5 x 0.1), represents the number of bacteria in the tube of the bouillon before its inoculation; while the results gained from the other plates, multiplied by 50, show the various inhibitory effects of varying lengths of exposure. These experiments must be several times repeated, or several series must be undertaken at the same time, in order to give reliable data.

After determining the antiseptic power of a substance as the above investigation will reveal it, it is very necessary to determine whether it is poisonous or not. This is determined as follows: A given substance for example X again, has been found to possess antiseptic, *i. e.*, bactericidal virtues in a proportion of 1 to 1,000. A rabbit weighing a thousand grams, as the average rabbit will weigh, or thereabouts, has injected subcutaneously one gram, in solution, of this same X; into another rabbit another gram is injected into the peritoneal cavity, while it is injected into a third by the intra-venous method. Each rabbit has now received $^1/_{1000}$ of its weight of X, and it remains to be seen whether the living animal can survive this strength any better than could the bacteria. If not, then X is to be considered *toxic*, and its *relative* toxicity is to be determined by further experiments conducted after the same fashion. If it can, then we have at last found that long desired substance which is parasiticide to bacteria, but with which the living organism can be impregnated in strength sufficient to kill such bacteria as may affect it.

But supposing that one gram of X is soluble only in 10 cc. of water, then our experimental rabbits must receive injections which are of themselves copious enough to injure or to kill. No rabbit can withstand the introduction at one time into the peritoneal cavity of 10 cc. of fluid. In such a case we take a smaller animal, for instance a white mouse, one such as will usually weigh 20 grams. This mouse must receive an intra-peritoneal injection of $^1/_{1000} \div 20 = ^1/_{50} = 0.02$ gr. This amount of the same X would equal $^1/_5$ cc. of fluid, which a mouse should easily bear in the peritoneal cavity. This method is, however, accompanied by difficulties. If we are experimenting with a strong antiseptic like a mercuric chloride, it can only be used in very weak solution, the strongest of which can be used only in $^1/_{500}$ strength, otherwise it would act as an irritant or even caustic, and so prevent the results we desire to obtain.

This determination of the poisonous properties of X is essential if we desire to so saturate the system with the substance that its antiseptic properties shall be exerted throughout the body, and this method of determination must be carried out with great nicety. According to Behring, we must make out, not only the relative, but the *absolute toxicity* of a given substance; its absolute toxicity being the proportion in which it will kill an animal, its relative toxicity the proportion in which it will kill bacteria.

Until the present time no substance has been discovered whose absolute toxicity is not greater than its relative. In other words, we have not yet discovered that which will not kill in the animal in $^1/_4$ or $^1/_5$ of the proportion required to kill bacteria. When we have discovered that one of which this cannot be said, we shall have learned to conquer sepsis. In many respects the serum of certain animals most nearly approaches this desired substance, but this only for certain bacteria. It is, for example, known that anthrax bacillus will not grow upon rat-blood serum, although it will upon serum from other animals. Streptococci will not grow on calves-blood serum—only on rabbit-blood. Within the past few years numerous investigations have been made regarding the antiseptic properties enjoyed by blood serum, from which it would appear that it affords the greatest protection which our systems enjoy to have circulating in our blood serum of this healthy character. To discuss this matter would lead us too far from the subject in hand, and is a matter to be followed out upon some other occasion.

Studies like these were begun ten years ago by Koch, who himself carefully tested some two hundred different substances. He then turned over the work to Behring, who has investigated half as many more. Only very recently has any statement emanated from the master or his assistants indicating that any such substance had been discovered. Recent utterances of Koch imply that he thinks he has at last found it, at least so far as animals are concerned, and he there publicly announced that he was ready to begin experiments with patients. His results remain to be heard. If he has been as careful and reliable in this work as in everything else which he has undertaken, we are on the eve of a fresh era in therapeutics.

The writer wishes here to express his personal indebtedness to Dr. Behring, of the Hygienic Institute in Berlin, as well as to his brochure "Ueber die Bestimmung des antiseptischen Werthes chemischer Präparate," etc. *Deutsche med. Woch.*, 1889, Nos. 41, 42, 43.

EXPERIMENTS WITH PYOKTANIN.

Applying now this method to present purposes permit me to report some investigations which I made last summer relative to one of the most recent candidates for bactericidal notoriety. During the meeting of the German Congress of Surgeons, (1890) there was exhibited by the Darmstadt house of Merck, a new antiseptic for which such claims were made as to stamp it—allowing for their truth—as a most important addition to the already large list. It was acknowledged and advertised to be an aniline derivative, but beyond this, at that time, nothing was told us of its *constitution* and its fanciful name, which had been protected, was calculated to reveal nothing. The improbable claim was made for it that it was capable of healing existing inflammations, and especially in wounds and ulcers. Also that it was perfectly innocuous, while its bactericidal properties were lauded as excelling those of sublimate. Along with circulars extolling its worth were sent out the brochure of J. Stilling, entitled *Anilin-farbstoffe als Antiseptica*, published just before the Congress. Something of his views may also be gathered from the following statements taken from a paper by Stilling, published in *Merck's Bulletin* (N. Y.) of June, 1890:

> I have discovered that certain groups of colorific *coal-tar derivatives* possess all the properties to be demanded of *a really good medicinal disinfectant*, which shall not alone prevent infection, but which must also be charged with the task of successfully combating ready-developed purulent processes; and that almost all the known pathogenic micro-organisms—anthrax bacilli and pyococci(pus-cocci)foremost among them—readily accumulate such colorants within their own bodies, just as

> larger plants do, and succumb to their toxic agency. Anthrax bacilli, pyococci, etc , as may be readily observed by the microscope, imbibe those colorants like a sponge; so that the bacteria may be noticed as being already deeply dyed before any of the colorific liquid itself becomes discernible in the field of vision; and the moment the intensive coloration is accomplished, every swarming motion ceases: the cell dies!

Although the specimens then exhibited were not allowed to be distributed, Herr Merck kindly sent me from Darmstadt some samples of the various preparations of pyoktanin which he was preparing for the market. With these, I at once began a study of its value, working along the lines already laid down in the earlier part of this paper, and with the kind advice and assistance of Dr. Behring.

Pyoktanin is furnished in two colors, *blue* and *yellow*, of which the former is much the more soluble. Of each of these a 1 to 1,000 solution was made.

In the following tables where a growth was found it is so indicated by the sign +, while the failure to grow or to develop is indicated by —.

I. Hanging drop cultures (bouillon) of anthrax, with yellow pyoktanin, at 37° C.

	1ST DAY.	3RD DAY.
Control	+	
1-7,000	+	+
1-3,500	—	+
1-1,400	—	—
1-700	—	—
1-500	—	—

II. Ditto with staphylococcus pyog. aureus.

	1ST DAY.	3RD DAY.
Control	+	
1-7,000	+	
1-3,500	+ ?	+
1-2,500	—	+ ?
1-1,400	—	—
1-700	—	—

III. Ditto with streptococcus pyogenes.

	1ST DAY.	2ND DAY.
Control	+	
1-7,000	+	
1-3,500	+	
1-2,350	+ ?	+
1-1,750	—	—

IV. Hanging drop cultures of anthrax, in *serum*, with yellow pyoktanin, at 37°C.

	1ST DAY.	2ND DAY.	3RD DAY.
Control	+		
1-7,000	+		
1-3,500	+		
1-2,350	?	+	
1-1,750	—	?	+
1-1,200	—	—	—

V. Ditto, with staphylococcus aureus (calves serum).

	1ST DAY.	2ND DAY.
Control	+	
1-7,000	+	
1-3,500	+	
1-2,350	?	+
1-1,750	—	—

These experiments were all made with the yellow pyoktanin. Similar work with the blue variety showed that it was more active, nearly doubly so, in fact. It is unnecessary to give the tables here after this statement.

Spore-thread cultures were next made, of which the following table will serve as a sample:

VI. Spore-thread cultures of anthrax (hanging drop) in bouillon, with blue pyoktanin, at 37° C.

	1ST DAY.	2ND DAY.	3RD DAY.
Control	+	Spores.	All spores.
1-80,000	+	+	
1-40,000	+	+	
1-20,000	—	+	+
1-10,000	—	—	+
1-5,000	—	—	+
1-3,500	—	—	—

Next a series of tubes of agar were impregnated with various proportions of yellow pyoktanin and cultures were attempted with the following results:

VII. Cultures of anthrax in agar, with yellow pyoktanin in proportions following, after 48 hours, at 37° C.

Control	+	
1-20,000	+	
1-10,000	+	
1-5,000	+	
1-2,500	+	Bacilli still abundant, only with relatively fewer spores.

VIII. Ditto, only with staphylococcus aureus.

Control	+
1-20,000	+
1-10,000	+
1-5,000	+
1-2,500	+

As a variation of this experiment I allowed a 1-1,000 solution to stand on top of a pure culture of staphylococcus aureus for 48 hours, then poured it off and transferred from this to a fresh tube. In 24 hours there was a luxuriant growth; showing that even 48 hours' exposure after this fashion failed to destroy this species.

IX. Next 5 cc. sterilized bouillon were inoculated with anthrax and carefully shaken. Solution of yellow pyoktanin was added till the preparation stood 1-1,400. (This was examined after 24 hours at 37° C., and no evidences of growth were found).

A. After 5 minutes' exposure a second tube was inoculated from this. In this tube *A*, after 24 hours in the thermostat, there was no growth perceptible; after 48 hours there were a few threads without spores.

B. After 2 hours a third tube was inoculated. In this, after 48 hours, there was no growth.

C. After 24 hours a fourth. In this, after 48 hours, no growth.

X. Same, except with staphylococcus aureus. In the original tube, 1-1,400, after 24 hours there was abundance of zoöglœa masses.

A. (5 minutes). In 24 hours rapid growth.

B. (2 hours). In 24 hours abundance of single cocci; in 48 hours zoöglœa masses.

C. (24 hours). After 48 hours abundant growth.

XI. Same, except with streptococcus pyogenes.

A. In 24 hours slight growth, which after 48 hours became abundant.

B. After 24 hours nothing; after 48 hours evident growth.

C. After 48 hours nothing.

XII. Streak cultures of anthrax on agar, with yellow pyoktanin in following proportions, after 48 hours in thermostat at 37° C.

Control	Typical growth.
1-2,000	Growth, but not so rich.
1-1,000	Limited growth.
1-750	Still more restricted.
1-500	Perceptible only along the streak and in good light. In the condensation water in the tube bacilli appear to have grown with considerable freedom.

XIII. Ditto, but with staphylococcus aureus.

Control	Typical growth.
1-2,000	Same.
1-1,000	Same.
1-750	Limited growth.
1-500	Only slightest appearance at isolated points. In the condensation water cocci have multiplied, but not in abundance.

The last results noted in XII and XIII would seem to imply that the agar holds the material and that the condensation water had lost its proportion of the same. Numerous coagula or flashes in the agar were more deeply stained and may have taken up an undue proportion of the dye by selective affinity.

XIV. Experiments to determine absolute toxicity.

For this purpose a solution of 1-100 of yellow pyoktanin, since, this being weaker than the blue, if this were absolutely toxic the other could be considered more so.

a. A rabbit weighing 1200 grams received 0.03 in the abdominal cavity (in 3 cc. water). At the same time under its skin 0.03 more;—*i. e.*, in all 0.06, $=^1/_{16}$ gram. This was equivalent to one twenty-thousandth of its weight of the drug. This produced temporary toxic symptoms, from which it recoved with apparent difficulty.

b. A second rabbit of same weight received three times the same amount, say one seven-thousandth of its weight, and died in a few hours.

c. Two white mice, weighing each 15 gr., received $^1/_4$ cc. of 1-100 solution, in abdomen; *i. e.*, one six-thousanth of their weight, or only one-fourth of what they should receive providing they could tolerate the drug in proportion of 1-1500. One died in $1^1/_2$ hours; the second barely recovered.

d. This second mouse, three days later, received a second dose of one three-thousandth of its weight under the skin of its back; it died soon after.

e. A mouse received one three-thousandth of its weight subcutaneously. Twenty hours later, having apparently recovered, the dose was repeated, after which it soon died. Two others received, each, one six-thousandth in the back; 24 hours later one was in condition of tremor and spasm and soon died, while the other was less affected, but died after some 40 hours.

f. Another mouse received one twenty-five-thousandth of its weight, and, 20 hours, appeared recovered; then it was given a three-thousandth more, and soon died.

g. Another mouse, which received one fifteen-hundredth of its weight, subcutaneously, died very quickly.

From all of which it appears that yellow pyoktanin must be present in strength of at least 1 to 1,500 before it can be considered an antiseptic, and the solution must be even stronger than this to prove reliable. Furthermore, that in proportions in which it can be considered relatively toxic, *i. e.*, to bacteria, it is absolutely toxic to animals;—which facts relegate it to a very low position among antiseptics, and seem to disprove all claims as to its great merits. I did not long pursue my investigations concerning the blue variety, since it was quickly found that it gave scarcely any different results from methyl violet and some of the other aniline dyes, which had been already tested in the Berlin laboratory, and found not to be at all reliable when in weaker proportions than 1-3500 or thereabouts.

Moreover it has since appeared that blue pyoktanin is nothing but methyl violet free from arsenic, or chemically pure, while the yellow variety is merely one of the yellow aniline derivatives freed from deleterious admixture. The protection of these substances by trademark, and the secrecy observed on their introduction, would therefore appear to be merely a trade subterfuge.

I have been lead to detail my experiments with the material not merely as illustrative of a method, but because numerous articles have recently appeared with reference to it, in some of which the writers appear to have allowed their verdicts to be influenced by what the manufacturers have claimed for it rather than by anything like a scientific test of its genuine value.

I would not wish to be understood as inveighing against a certain well-known value which most all of these aniline preparations have in common. In 1872, Dr. Chas. Curtman, of St. Louis, made known the fact that they possess antiseptic properties, and common experience has since confirmed his statement. Stilling has gone so much further as to assert that they are absolutely non-poisonous, a statement which is far from justified by facts. Behring has pointed out the remarkable correspondence between them all, that their absolute toxicity is four or five times as great as their relative toxicity, or their antisepticity, which is corroborated by my own results given above. *In fact this is true of well nigh every antiseptic tested;* and though reactions between a given substance and a particular species may show, now and then, wide variations, the general statement is beyond controversy. Indeed we see the same thing in other directions; thus (*vide supra*) anthrax bacilli will not grow on blood-serum from the rat, and Metschnikoff's vibrio can scarcely be planted in the blood of living mammals, though pigeons succumb in a day or two.

Referring back to our particular subject I would like to quote from Stilling's paper (loc. cit.) the following directions for its use in surgery and ask you to contrast them with the results of experimental tests.

The surgical antiseptic methods by means of *Pyoktanin*, I conceive to be carried out as follows: The instruments are to be simply well cleaned; or, if extra caution be desired, to be steeped, for some time preceding the operation, in a weak solution of *Pyoktanin*,—say about 1:10,000 or 1:20,000. After the operation the wound is to be washed with a somewhat stronger solution of the same,—say 1:5000 to 1:2000. The needful stitching is to be done with silk impregnated with a 1:1000 solution of the same. Finally, the dressing of the wound would consist of antiseptic cotton and antiseptic gauze, also prepared by steeping in a 1:1000 solution of the same medicament. Thus prepared dressing materials are not only reliably *aseptic*, but also reliably *antiseptic*, and even *disinfectant;* for the slightest *secretion* of fluids within the territory of the operation must at once cause an *absorption* of a sufficiently concentrated solution of the *Pyoktanin.* Purulent developments in *puncture-channels* ought certainly not to be possible under this prophylactic *Pyoktanin* treatment.

I have no hesitation in asserting that even the blue pyoktanin —the stronger—can not be relied on in strengths above indicated for purposes claimed.

Another kind of claim was made for the material, which includes its stimulating and other desirable properties, by which it is expected to subserve useful clinical purposes. As an injection in gonorrhœa, I have had no experience with it, but find that most of those who have tried it have met with disappointment. Upon granulating surfaces it does appear to be stimulating and to exert a desirable effect, but no more so than other substances within easy or easier reach, and its stain is often undesirable. In ophthalmological practice it appears also to have scarcely come up to the requirements of the day. On the whole, then, it has but few qualities by which we are to commend it above numerous other drugs of its general class, while in all that may answer to the more scrupulous demands of aseptic surgery it has proved in my hands—as in those of others who have tested it from the purely clinical standpoint—disappointing.

RECENT LITERATURE CONCERNING PYOKTANIN.

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Merck's Bulletin, New York. June, 1890.

New York Med. Jour., 1890, August 23, p. 204.

University Med. Magazine, October, 1890, p. 38. *With Bibliography, q. v.*

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LECTURE VI.

TETANY—TETANUS.

SYLLABUS. *Tetany.*—Definition and theories of its causation. Frequency after thyroidectomy. In the past has often been mistaken for tetanus. Semeiology and symptomatology. Researches concerning the thyroid body. Experiments with its extirpation and transplantation. Relationship of tetany to myxœdema and cachexia strumipriva. Acute mucin poisoning. Deductions as to the safety of certain operations on the thyroid.

Tetanus.—Consideration of the wounds, the wounded and their environment, when dealing with the subject. Class of wounds most often infected. Predisposing causes and circumstances of age, sex, color, climate and mental condition. Influence of weather and other conditions of locality. Tetanus hydrophobicus and tetanus neonatorum essentially the same as the traumatic form.

Theories as to its causation. Theory of its nervous origin. The humeral theory and that of its zymotic origin. Discovery of its specific microbe by Nicolaier, and confirmation and elaboration of his work by Kitasato. Description of the bacillus of tetanus. Discussion of its peculiarities and specific action after inoculation. Deductions as to possible treatment of the disease.

THOUGH tetanus and tetany are not merely similar in name, but present many characteristics which might lead to mistaking one for the other, there is, nevertheless, such a wide etiological difference between them that a clear differentiation is of the greatest importance, not merely for the sake of accuracy, but for the credit of surgery and the welfare of an important class of patients, *i. e.*, those suffering from enlargements of the thyroid.

Both occur as sequels of operative interference, and if tetany is so infrequent as never to be seen by some, it may be experimentally produced and studied almost at will.

Tetany may be described as apparently a neurosis, manifested especially by tonic spasms, particularly of the extremities, and an increase of mechanical and electrical excitability of peripheral nerves. It is pathognomonic of the disease that these spasms may be produced by compression of one of the great arterial or venous trunks.

It was described first by Corvisart and Trousseau, and then more fully by Erb and Chvostek. It occurs spontaneously in less severe form in pregnant and nursing women, in children after exposure to cold, or after such intestinal lesions as may be produced by typhoid or by parasites; also among young apprentices to certain trades. It occurs also in endemic or epidemic form. But what interests us most here is that it sometimes follows certain operations, and extirpation of the thyroid in particular, and then constitutes so serious a complication that a large percentage of patients succumb.

It has been described under various names besides tetany, as, *e. g*,, tetanella, idiopathic muscular spasm, carpo-pedal cramps or spasms, etc. It is certainly a functional neurosis, comprising spasms of muscles in a pretty regular order or rythm. Patients do not lose consciousness.

It was considered by Herz to be due to spinal anæmia, while Jacobi, on the contrary, attributes it to meningeal hyperæmia, and Gowers explains it on the hypothesis of a primary lesion in the primary cells of the cerebro-spinal tract. While it is certain that its pathology and symtomatology are still obscure, it will be shortly seen that a notable advance in its experimental study has been recently made.

According to Weiss (*Ueber Tetanie*, "Volkmann's Samml. klin. Vort.," No. 189), it was noted as a post-operative phenomenon in Billroth's clinic. Later it was noted and remarked upon by Schönborn, Albert, Nicoladoni, Mikulicz, Gussenbauer, Corley, Szuman, Kocher, Kothman, Higguet and others, and has recently been made the subject of a careful experimental study and an elaborate essay by von Eiselsberg (*Ueber Tetanie in Anschlüsse an Kropfextirpation*, Vienna, 1890), to which I am greatly indebted, and from which I have largely drawn.

The most striking characteristic about tetany is the peculiar severity or malignity which it exhibits when occurring as a sequel to thyroidectomy. Thus Eiselsberg refers to twelve such cases in Billroth's clinic out of fifty-three total extirpations, of which eight died, while in two the disease assumed a chronic character, and only two finally recovered. To its severity and its fatality is largely due the unfortunate confusion of terms and clinical pictures, by which so many deaths after total extirpation of the thyroid have been described as due to tetanus. It is of importance, then, to differentiate accurately between the two diseases.

The symptoms of post-operative tetany may supervene almost immediately after the effects of the anæsthetic have disappeared, or may be delayed so long as ten days. Usually prodromal symptoms give warning of what is coming; such as malaise and a combination of muscular weakness, with a sensation of muscular stiffness. Sometimes these sensations are quite absent and the outset of the disease is equally violent and surprising. Two signs which may be usually early elicited are so characteristic, so diagnostic, that they deserve great emphasis.

The first is Chvostek's. A slight tap upon the side of the face, over the point where the facial nerve emerges from the parotid, suffices to call forth a sudden spasm of that side of the face. The second—Trousseau's—is the spasm of an extremity, which may be produced by compression of its principal blood or nerve supply for a brief period of time, from a few seconds to a few minutes. The first sign is easier of production, is elicited without detriment to the patient, and is pathognomonic; while the second is of no greater value, and may be followed by pain, and its frequent repetition certainly does serious harm to the patient.

The muscles of the face are those commonly first affected; then those of the upper extremity; they are always more marked in the arms than the legs, and sometimes the latter seem to escape. The position of the hands and fingers is usually that seen in cases of irritation in the course of the ulnar nerve; the elbow somewhat flexed, the hands flexed to the ulnar side, the fingers bent at the metacarpo-phalangeal joints, thence straight and stiff, the thumbs bent into the palms. This position of the hand and fingers is not invariable nor pathognomonic, but is that usually seen. Sometimes the fist is doubled up with the thumb between the first and second fingers. The muscles of the forearm are hard, and sometimes a little tremor may be perceived. It is always difficult to overcome the muscular spasm. In severe cases the hands are usually held with their backs pressed together. When the lower limbs are affected the legs are usually stiffly extended, with strong plantar flexion of foot and toes. With all this muscular spasm there is more or less pain in the affected parts, with temperature usually considerably elevated. Such attacks may last from two to fifteen minutes or more, but they do not occur with nearly such frequency as the convulsive seizures of true tetanus, and it will be seen that there are other wide differences in the onset and march of the two diseases.

Nevertheless, in the most severe form of tetany there may be such contortion of the facial muscles as to resemble the "sardonic grin," and which would, of course, destroy the significance of Chvostek's sign. Tonic cramp of the abdominal muscles is not unknown, especially of the recti, and one may even see a certain degree of opisthotonos.

Dyspnœa may be caused by spasm of the diaphragm or thoracic rigidity, and cyanosis may be the result of cervical spasm. In some cases the patients give shrill cries; others speak with great difficulty. Deglutition is sometimes difficult. Finally in the gravest cases consciousness is lost; and usually at such times spasm relaxes. Death never occurs in the height of the disease, usually hours or days later.

Autopsy gives only negative findings; only twice Weiss found some slight disturbance in the gray matter of the anterior horns in the medulla.

Some peculiar features have been noticed in individual cases. Thus in one of Billroth's cases the patient was four months pregnant at the time of the thyroidectomy. Normal delivery at term was in no wise interfered with, although for *nine years* she suffered from tetanic seizures, during which Chvostek's and Trousseau's signs could also be easily evoked. For the latter a very brief compression of the ulnar nerve sufficed. Overwork or excitement, particularly in cold weather, seemed to precipitate these attacks. Her temper appeared less equable than before the operation, and she was at times found almost uncontrollable. Before the operation, too, she had suffered spontaneous loss of hair and nails; these were afterward as spontaneously restored.

Another and younger woman recovered, but long remained subject to mild attacks, which occurred much oftener in cold than in warm weather. After a couple of years she had no seizures properly speaking, but the phenomena described by Chvostek and Trousseau could be elicited at almost any time.

Weiss has described (*Allg. Wiener Med. Zeit.* 1885, No. 37.) an atrophy of those groups of muscles most involved in the spasms, as a sequel of tetany, though not of that observed after thyroid extirpation. So also falling of the hair has been noted by Kocher (*Arch. f. klin. Chir.* 1883) as an accompaniment of cachexia strumipriva, and by English writers among the symptoms of myxœdema.

In one of the marked fatal cases, and in two of the others, a great temporary improvement was noted after a profuse sweating. Whether this might be of service as a hint in the therapeusis of the affection is a question worth considering.

It will be noticed that all of Billroth's twelve cases were females. Of the eight fatal cases, as detailed by Eiselsberg, I have tabulated the following information: (See table, p. 130).

Though so rare among males the disease is not unknown among them, since Mikulicz has reported two cases and Higguet one.

No treatment seemed to be of avail, and nothing seemed to mitigate the intensity of an attack. The internal use of chloral with the subcutaneous exhibition of morphia seemed most satisfactory. In view of a remark made above, I would suggest the expediency of trying pilocarpine as a diaphoretic.

When these and similar cases are critically studied it appears that their ætiology is inseparably connected with the total removal of the thyroid. They were in no wise nor remotely septic. In the eight fatal cases above alluded to only once was there the slightest suppuration in or about the wound. So with the cases reported by others; wound disturbance of any kind was the rare exception. To be sure in the very few cases reported where pus has collected in the wound the violence of the symptoms increased, but pressure upon the scar at almost any time would have the same effect; and in other cases it was noticed that a constrained position in bed affected one patient in the same way, and in another, apparently about recovered, a warm bath precipitated a violent attack.

Age.	*Attack Began, Days After Operation.*	*Lived How Long, After First Attack.*
12	Fifth.	Three months.
18	First.	Three days.
39	Tenth.	One day.
64	Ninth.	Eight days.
17	Second.	Seven months.
23	First.	Three days.
36	Fourth.	Four days.
32	First	One month.

Injury to the recurrent laryngeal nerve does not explain these cases, since this nerve is practically always injured in these operations. We are confronted with the following most significant figures: After 53 total extirpations it occurred 12 times; after 11 partial extirpations it did not occur at all. It has occurred twice, once to Szuman, once to Billroth, to see mild cases of tetany after nearly complete removal of the thyroid body. The inference, then, is unavoidable that in some way, not yet understood, the removal of the thyroid brings about the curious phenomena collectively termed tetany. *How* or *why* this is the case is a problem to be solved—if at all—only by experiment. This is made the more difficult by lack of exact knowledge of its function.

The names of A. Bardeleben, Schiff, Zesas, Colzi, Wagner, Albertoni and Tizzoni, Sanguirico and Canalis, Fuhr, Munk, Horsley, Carle and others less well known, have heretofore figured prominently in researches upon this organ. As the result of their labors it has been pretty well settled that in cats and dogs removal of the healthy thyroid provokes a constant diseased condition which is fatal; while sheep, rabbits and rats tolerate it without harm. Further, when it is made *a deux temps* the symptoms only appear after removal of the second half. Extirpation of a lateral half only is seldom provocative of disturbance, while Wagner, Horsley and Rogovitsch have seen a compensatory hypertrophy of the remaining portion. (Vid. Sutton's *Dermoids*, p. 83–4.)

Schiff went further and experimented with transplantation. It is now known that this peculiar organ, or ductless gland as it is often called, possesses tbe peculiar property of usually first quickly contracting adhesions in any new tissue in which it may be placed, and then later of establishing for itself an adequate vascular supply with, presumably, more or less restoration of its function.

Schiff claimed that when an animal, into whose peritoneal cavity the thyroid of another of its own species had been transplanted, subsequently had its own thyroid totally removed it did not develop these peculiar symptoms. But these results claimed by Schiff have been positively denied by others, and certainly need confirmation. At all events it seems pretty clear that dogs and cats very seldom survive removal of the entire thyroid, and that in those who do accessory thyroid bodies are found. It was Fuhr who especially determined this matter, to disprove the claims of Kaufman and Tauber; and he further showed that no amount of irritation of the recurrent nerve sufficed to provoke tetany—only total thyroidectomy would produce it. Horsley has shown that virtually the same obtains in the case of monkeys, who develop tetanic symptoms and fall into a condition of myxœdema, in which mucin is found in considerable quantities in certain tissues and in the blood.

In order to better determine the influence of the thyroid relative to these peculiar nervous phenomena Eiselsberg made experiments on a series of 100 cats, having selected this animal because it seems to be free from accessory thyroids whose presence, by subsequent compensatory hypertrophy, might vitiate the results.

In one series he made total extirpation 17 times. Only once did suppuration occur, the other 16 wounds healing *per primam*. All these animals developed tetany; the youngest displaying its characteristic signs almost immediately after awakening from the narcosis, the others in from one to three days. All died of the disease. The symptoms in animals consist of tremors and muscular spasms which show themselves particularly as the creatures rise from the recumbent position or still more from the dorsal. Dyspnœa is frequent. Then tonic spasm of the extremities supervenes, and this can be produced almost at will by tapping the limb over the greater nerve supply. During pauses they are usually quiet and apathetic. They usually die in spasm. The course of the disease is usually about a week, but it may be fulminating and kill them in a day. Loss of appetite and rapid emaciation are conspicuous. The act of deglutition frequently provokes an attack. Free flow of saliva is often noted; during this there is sometimes temporary improvement. The limbs often assume rigid positions, reminding one of catalepsy.

Nine times total extirpation with transplantation was tried—once under the skin of the neck, twice under that of the belly, twice between muscles, twice in the peritoneum, and twice as Schiff did it. Seven times out of nine these wounds healed *per primam*. All nine died of tetany.

In 1887 Ewald reported (*Ber. klin. Wochschft., 1887, No. 11*) that after hypodermic injections of thyroid juice into healthy animals, some disturbance—lasting 1—2 hours—was produced. But according to Horsley this has no different effect from other tissue juices which contain some fibrinogenous poison. With this in mind Eiselsberg made five total extirpations, after which a strong extract of the thyroid was injected under the skin, without any apparent effect. In two other animals he substituted a small dose of morphia, by which both animals were made more quiet, but all seven died of tetany. He then tried a fourth series of sixteen, extirpating only a lateral half. Two animals died of infectious pneumonia, the other fourteen all recovered, without any appearance of tetany. In eleven others the extirpated half was transplanted into the peritoneum, with the same negative result.

Twice he followed Schiff's experiments, and extirpated first one half and then the other, transplanting the second half into the peritoneum, and both animals died of tetany. Nine times this experiment was so varied that *the first half* removed was transferred, while the other half was extirpated from 3 to 21 days later. Eight of these animals showed perfect wound healing, but died of tetany; only one of these, an old and large animal, with a period of 3 weeks intervening between the two operations, recovered without disturbance.

These results correspond exactly with Carle's obtained on dogs. In four of this last series of nine cases it is noteworthy that between the first and second operations a considerable hypertrophy of the undisturbed half had taken place, and when this second and enlarged half was taken away, in each instance the tetany was of the fulminating variety. Only once out of four other cases in which the first half was transplanted between the peritoneum and its overlying fascia, did perfect fixation and organization—*i. e.*: vicarious restoration of function (?)—take place; the other three died of tetany.

Seven other experiments, by which more than half of the total thyroid mass was removed, seem to demonstrate that when four-fifths of this body is taken away, tetany is the almost inevitable result. In sixteen other animals vascular exclusion of the thyroid was made by ligation of all its vessels. All of these developed tetany, and all but four died of it; the four gradually recovered. When the two halves were thus excluded at intervals of six weeks, there was no apparent effect.

These numerous experiments certainly seem convincing though the obvious inference is not in accord with the views of Munk and Drobnik, who are disposed to regard the tetany as due to irritation in and about the wound upon the large nerves closely adjoining, and who ascribe to suppuration the *role* of being the irritant factor. It will be seen that 87% of wounds in those animals which Eiselberg operated upon healed without suppuration, and that this union *per primam* did not seem to interfere with the onset of tetany. Moreover, Horsley, Fano, Ewald and Weil have abundantly shown weaknesses in Munk's chain of argument, and have apparently disproved his contradictory statements, showing the fallacies of his reasoning and the inaccuracy of his methods.

Although it takes us away from our primary subject, which is rather a discussion of the ætiology of two diseases presenting certain points of resemblance yet widely different in pathogeny, still we may with profit consider for a moment what relation tetany, following thyroidectomy, bears to myxœdema and to cachexia strumipriva, following the same procedure. The two latter are eminently chronic maladies, while the former is essentially acute. We are largely indebted in this consideration to the Myxœdema Committee of the London Clinical Society (Appendix to their Trans., 1883), and especially to Horsley's experiments upon apes. This investigator saw sometimes a rapidly fatal tetany, which has been spoken of as acute experimental myxœdema, while in other cases there developed slowly the well known signs of the common form, depending very largely upon the temperature at which the animals were kept, since the colder the environment the more quickly they died, and with more acute symptoms. In the first stage of myxœdema there is a marked increase of mucin secreted by the salivary glands, intestines and bladder, while on autopsy it is found in the blood and in abnormal quantities in certain tissues. The influence of temperature is beautifully demonstrated in an instance reported by Horsley. A sheep underwent total extirpation, and remained apparently well for twenty months; he was then, after shearing, exposed to cold, after which he developed acute symptoms and died a typical death. From all of which it appears that tetany and myxœdema are, as it were, interchangeable diseases; dependent on the same causes, differing only in march and course. It follows from this that the thyroid is an organ not only of peculiar function, but that it is one of the most indispensable parts of our bodies. Of several hypotheses which have been advanced to account for its peculiar importance, that which seems best to explain the facts, and, indeed, perhaps the only one tenable, is that it has to do in some way with the transformation of mucinous substances which when allowed to collect in the system certainly are injurious and even fatal. As corroborating this view, we know a peculiar bronchial catarrh which these patients occasionally present, with its tenacious mucinous secretion; further that with the subsidence of this elimination the disease is commonly augmented.

Furthermore, that with profuse salivary or sudoriparous excretion amelioration occurs, and that when excretion is hindered, as by cold, the symptoms are at once changed for the worse. It appears that by such symptomatic discharges the flooding of the organism with mucin is prevented. Finally, the very common colloid, or, more exactly, mucoid degeneration of the thyroid body has a significance which must not be overlooked; as if, according to Eiselberg, when this organ can no longer bring about the proper conversion of mucin (or its allied substances) it collects it in reservoirs in the shape of colloid material, which is, at least, difficult of resorption, and so keeps it out of the economy.

These views gain credence also from the undeniable fact that excess of mucin is poisonous to the system, and this has been beautifully demonstrated by Wagner. He injected mucin which had been carefully extracted from the salivary glands of cattle, into cats, and produced thereby typical tetany.

The occurrence of idiopathic tetany appears to have much to do with meagerness of diet or improper nutrition. Neusser has called attention to a certain similarity between pellagra, as he studied it in Austria and Roumania, and epidemic tetany among school children. Each appears to be in no small measure an auto-intoxication brought about by unwholesome food. Most interesting and important in this connection is Gerhardt's discovery that tetany sometimes follows dilatation of the stomach, with its train of fermentative mal-digestive disturbances.

Obviously, certain difficulties present themselves in accept-ing these views. Why should certain animals display so violent manifestations after thyroidectomy, while other species or genera are scarcely or not at all affected? Why should the carnivora belong to the former class, and the herbivora to the latter, as to a large extent they do?

Beyond stating that the herbivora appear to be exempt from the acuter manifestations, we can give no answer to such questions unless it be found in the nature of their diet. It is of interest here that at least one patient who made a good recovery after thyroidectomy noticed a notable change in his own appetite, since he reported to Eiselsberg that he had lost all wish for meat and had become a vegetarian (loc. cit. p. 35, note).

Another query naturally arises here. Why do some persons to all appearances completely recover after thyroidectomy, while others succumb quickly to acute tetanic manifestations, and yet others fall into the most sad condition of myxœdema? As yet this can only be partially answered. Yet it is known that in youth the thyroid plays a more important part than in latter adult life. It is also quite sure that when we attack the thyroid it is because it is no longer in a physiological but a pathological condition, and when we draw inferences between clinical experiences and experimental results we must bear this in mind. Moreover, it appears safer, so far as the disease at present considered is concerned, to remove a cancerous thyroid than a goitre. Moreover accessory or supernumerary thyroids are frequently found, often at points where they are difficult of recognition, as behind the larynx, at the root of the tongue, etc., and when present they can of course assume an importance begotten of necessity. To this I might add the possible assumption of function, in certain cases, by such correlated tissues as the tonsils or other lymphoid tissues, or possibly even the bone marrow, although nothing definite is yet known upon the matter.

Although it bears little if at all on the pathology of tetany I deem it quite advisable here to introduce a very brief notice concerning some recent and very important studies concerning the curability of myxœdema, taken in the main from a recent note in the *Therapeutic Gazette*, (Oct. 1890, p. 718).

Early in 1890, Mr. Horsley suggested that the disease might be cured by transplanting healthy thyroid tissue into the bodies of patients thus suffering. But it appears he was forestalled in the idea by Bircher, who related certain valuable results obtained by this method. He described an acute case in a female patient from whom, unintentionally, the whole gland had been removed. Severe symptoms supervening, Bircher in January, 1889, transplanted into the abdominal cavity a portion of an apparently normal tissue from a goitre. The immediate eflect was very happy and the patient returned to work. Three months later, however, it become evident that the transplanted portion had atrophied, as myxœdema again appeared and progressed. A second transplantation was then made with more lasting improvement, as the patient remained fairly well for nine months. At time of writing the symptoms had returned in very mild degree, but the beneficial effect was established indubitably.

In the *Brit. Med. Jour.* for July 26, 1890, Horsley reports that he had recently learned from Kocher, of Berne, that he attempted to obtain the same effect in 1883, by the same method, but that the graft was too soon absorbed. Further, that after hearing of Bircher's success, Kocher took up the subject again, in 1889, by transplanting, in two cases, half of a thyroid body into the abdomen, fixing it to the wall by sutures. In each case the gland was, after a time, "aseptically exfoliated." Then in three cases he put the gland loose in the abdominal cavity. The final results of these cases have not yet appeared, though at least one was grearly improved.

From these considerations Mr. Horsley thinks that the operation should be performed not only in cachexia-strumipriva, but also in myxœdema and sporadic cretinism. But whether the transplanted gland-tissue may better come from a human being or from an animal remains to be decided.

There is perhaps no *terra incognita* in physiology in which ingenuity of research and pains taking study may be better rewarded than that outlined in these few remarks upon tetany. It is a field wherein the interests of the pathologist, the clinician and the operating surgeon are common property, and he who properly harvests the seed already sown there may prove a benefactor to his race.

Etiologically the subject of tetany has nothing to do with that which must next engage our attention, namely tetanus. Yet. clinically they appear so closely related that those that ought to know better confuse them. Thus, I was informed, while abroad last summer, by a more than ordinarily intelligent physician that a well known European surgeon had lost so many patients from tetanus after removing the thyroid that he had been virtually forced to give up such operations. It required some pains to elicit the facts in the case, which simply were to the effect that he, like some others, had become discouraged on account of the proportion of cases which developed *tetany* after total extirpation of the thyroid. There would seem, then, to be no impropriety in proceeding at once to a consideration of some of the features of tetanus.

TETANUS.

Unlike tetany, tetanus is referred to in the oldest annals of medicine. One may find in Hypocrates, Galen and Celsus at least some indication of its principal symptoms, but its precise clinical history commenced with the end of the previous century, with the observations of Bajou and the grand work of Heurteloup which gives an excellent resume of the knowledge of his time. Fournier-Pescey extended this knowledge and showed the possibility of recovery. During the wars of the Empire clinical facts multiplied and we were given the accurate description of Larrey. It has remained for the second half of our own century to clearly discover the etiology and pathology of this disease.

Following the example of Richelot, in his Thesis of 1875, and of Mathieu, in his article in the Encyclopedic Dictionary, we must speak successively of the wounds, the wounded and the environment. First of all, any wound may present this complication, but some predispose more than others. The point of injury makes some difference. Wounds of the extremities, of the hands especially, seem more often to determine trismus than any others. Thus for Poland and for Yandell more than one half of the cases are due to traumatisms of the extremities. The character of the wound has been alluded to by authors as occasioning a predisposition. Thus gun-shot wounds, especially the lacerated and contused, and next perhaps the injuries received from machinery, seem to be the most grave. The most cleanly cut wounds seem to be the least often infected, although tetanus in the past has, not rarely, followed amputations. On theoretic grounds, referring to the parasitic origin of the disease, it is not difficult to understand why it should more commonly follow ragged wounds. Burns, whether accidental or provoked by the actual cautery or by chemical substances, and frost-bites, whether superficial or deep, have also caused the disease, and as is well known, it frequently follows ligature of the umbilical cord in the new born. The extent and depth of the wound are features without importance. The prick of a needle, a hypodermic injection, the bite of a serpent, the penetration of a thorn, the extraction of a tooth, piercing the ears for ear rings, vaccination, dilatation of the nasal canal, the removal of an in-grown nail, and other equally trivial accidents or operations have been followed by the disease. In the past such operative measures as the constriction of a nerve in a stump, or the ligature *en masse* of the spermatic cord, or of the pedicle after ovariotomy, have been forbidden for this reason.

The presence in the wound of foreign bodies, of bullets or fragments of weapons, of thorns, of needles, and of any other small foreign particles, seems to predispose toward the disease. It has been generally supposed that an actual break of the surface by which air might be admitted, was a prerequisite for the manifestations of tetanus, but evidence is very strong that this is not absolutely necessary. The well known case of Morgagni in which it followed a contusion of the back, and such a case as that reported by Verneuil where it was apparently produced by a violent effort to prevent a fall, as well as cases reported by Bouchut, Macleod and others, put this all beyond a doubt. Closed fractures and small luxations or dislocations have likewise been followed by tetanus. A case has been reported by Richelot in which it followed the dislocation of a finger, and in which dissection revealed the nerves stretched over the dislocated extremity of the phalanx like violin strings. Such cases, therefore, are not so very rare.

Out of 121 cases observed by Wallace, in the Indies, 13 were of this character. Here also may be properly emphasized the fact that it may not occur until after cicatrization of a wound. Thus Cooper, Annandale, Larrey, Langenbeck and others have reported incontestable cases of this kind. I have myself seen, in consultation with Dr. Norton, then of Buffalo, a case of tetanus which resulted fataly, and which followed some weeks after complete healing of a tarsectomy wound, in an adult, made for the relief of club-foot. The patient had so completely recovered as to be up and about his work, when he was suddenly seized with the unmistakable symptoms of the disease.

The wounded individual is more or less predisposed according to circumstances of race, sex, age and constitution. The colored race are always more liable than the white. The negroes, Hindoos, Malayans and the islanders of Tonga and Fiji show a particularly unhappy disposition. That negroes are particularly liable was abundantly shown during our Civil War, and that the inhabitants of warm countries seem the less resistant is shown by the fact that in various European wars the Italians and the French have suffered more than the Russians and the Austrians. One ordinarily speaks of tetanus as a disease of adult life, yet infants are by no means exempt; and in the tropics the trismus of the new-born has caused a high rate of mortality. It was said by one plantation owner that fully three-fourths of the infants born upon his plantation succumbed to the disease. In Jamaica, according to Fournier-Pescey, a quarter of the new born Negroes succumb within eight days after their birth, and in Mexico and in Senegal the proportion is at times equally great. The ulceration around the ligature of the cord, or the little wound inflicted during the rite of circumcision, are the common causes of tetanus among these new-born, although it must be admitted that their detestable hygienic surroundings and their excessive poverty are contributing causes.

Men are attacked much more commonly than women, doubtless because their occupations expose them to more injuries, especially in war, males being commonly ten times as liable, according to some of our best authorities,—except where climate, as above noted, especially predisposes. This difference is the more remarkable since parturition with its difficulties, and sometimes the necessary operative interferences, should make the disproportion less striking. In fact, much less serious injuries in the female have been followed by this disease. Thus, it has been known to follow amputation of the uterine neck, dilatation of the cervical canal by sponge tents, removal of polypus and ovariotomy.

Military surgeons have generally insisted that the mental and constitutional condition of patients figured largely in the etiology of the disease. Soldiers when worn out by fatigue or suffering from the disgrace of defeat or with their emotions vividly affected from any cause, are apparently more liable to the disease. The excitement of a sudden call to arms, of sudden discharge of cannon, even the whirring of bullets during the night, have been said to cause a shock which appeared to determine an invasion of the disease. Still, in 1870, says Mathieu, the besieged in Strasburg, Metz and Paris were affected with emotions even more vivid than those of the besiegers, and yet these last suffered more from tetanus; and thus after Waterloo the allied armies were less attacked than were the French, and so too in our Civil War not a single case was reported in the Confederate army, while the Federal troops lost 505 men from this source. Furthermore, those with visceral disease seem to be more subject to the disease. Malaria has also been supposed to be a contributing cause.

The influence of the environment is by no means the least interesting factor in the present consideration. The effect of climate is indisputable. Tetanus is *par excellence* a disease of hot countries. Guinea, Antilles, Senegal, Ceylon and Java have a reputation above all others. Military statistics show the same thing. In 1813 in Spain the English suffered in the proportion of one case of tetanus among eighty wounded men. In the East Indies in 1782 this proportion was doubled. In the war in Morocco there was one case of tetanus to nine hundred and twenty hospital patients of Spanish, and one to fifty-six of African birth. Apparently it is not heat alone which determines this intensity, so much as the combination of heat and humidity; still, quick variations of heat and cold, such as warm days and cold nights, seem to exert a great effect. The sudden fall of temperature after the battles of Dresden and Bautzen, according to Larrey, caused a large number of cases. The electrical disturbances which accompany violent thunder storms seem to exert an influence, as do also cold winds saturated with moisture, like those which come from off the sea or sweep down the valleys of large rivers. Curiously enough the wounded who have been cared for in churches have suffered more from this disease than those cared for in any other way. After the battle of Jena, tetanus attacked especially the wounded who had been carried into churches. In 1870 after the battle of Sedan it was those who were thus cared for during the combat and the following night who were mostly attacked.

Verhoogen and Baert have recently published a memoir, dedicated to the Royal Society of Medical and Natural Sciences of Brussels, in which they cite at some length the endemic character of the disease in warmer climates, and in which they show the occasional epidemic character of the affection in man and even in some of the lower animals, and they cite as among the most startling evidences of this character the remarkable experience of Thiriar. He was unfortunate enough to lose by tetanus ten cases of major operations before he determined the source of the infection to exist in his hæmostatic forceps. So soon as he thoroughly sterilized these by heat he had no further undesirable complications. If the disease can be so easily conveyed by instruments, the same is true of a midwife's scissors, and these latter may well be the cause of the terrible fatality of tetanus neonatorum of these same climates. These writers call attention also to the indefinite symptoms preceding the outbreak of the attack; the fever, the occurrence at times of epistaxis, the existence in many cases of a cutaneous rash resembling that of erysipelas, to the symptoms of kidney disease and the changes occurring in the kidneys, and to the enlargement of the spleen, as being all characteristic of the usual course of infectious disease.

The term *tetanus hydrophobicus* or *cephalic* tetanus has been applied to a somewhat peculiar manifestation of the disease first described by Bernard and Lepine.

When the injury by which the disease is provoked is located near the parts supplied by the cranial nerves the facial nerve has been supposed to be affected upon the same side; the lightest disturbance causes painful spasms of the neighboring muscles involved, and the pharynx and larynx, being virtually supplied by these nerves, when thus involved are so affected as to produce an intense dysphagia, with spasms of the glottis upon any effort to swallow even fluids; whence its misleading name of tetanus hydrophobicus. The poor patient suffering from these painful muscular spasms, which are provoked even by the sight of water or the thought of taking anything within the mouth, cyanosed, with spasmodic dyspnœa or temporary apnœa, presents a picture conforming well to the type imagined by the laity as that of a person in the last stage of hydrophobia.

Brunner has very recently experimentally studied this phase of the disease anew. He has determined that, in animals at least, the peculiar appearance of the face is due not to facial paralysis, but rather to a tonic tetanic spasm of muscles. This was made the more evident by a section of the facial nerve after appearance of this condition, whereupon it subsided at once. This is unquestionably the case also in patients thus affected, since it is impossible to understand how the parts supplied by the facial should be paralyzed while those supplied by the pneumogastric and hypoglossal should be thrown into violent spasm. (*Deut. Zeit. f. Chir*, xxx.)

With regard to the etiology of tetanus, two theories have in the past had their strong advocates, or perhaps, to express it more accurately, the explanations that have been offered in the past can be best grouped under two distinct headings, as first the nervous theory, and second the humoral. The significance and intensity of the principal phenomena of tetanus have always pointed us so distinctly to the nervous system as the most active agent in the production of the disease, that it is not at all strange that the primary irritation has been located in some part of this system. Under this heading, however, must be ranged such explanations as that given by Forbes, who attributed the poisoning to a successive production of creatin and lactic acid, in consequence of exaggerated tissue degeneration; this latter he considered due to excessive nervous activity, and this last he left unexplained. Such an hypothesis as an ascending nervous irritation due to lesion of the peripheral nerve filaments, is, perhaps, the simplest that would offer, and has had numerous adherents in the past. Besides this, there have been many who regarded the disease as due to an excitation of the spinal cord, and by this have explained the increased temperature, the tendency to asphyxia, and some of the other phenomena peculiar to tetanus. According to Brown-Sequard, it is a pathological reflex, having for its point of departure a peripheral nervous irritation, causing an undue functional activity in the superior portions of the medulla, which is followed by muscular contractions and elevation of temperature.

So far as the microscopic changes in tissues are concerned, there is much difference of opinion among authors. Rokitansky and Demme have discovered changes in the neuroglia of the white matter in the spinal cord, which, however, Leyden does not consider to be pathological. Other authors like Clarke believe in congestion and softening of the grey matter, Dickinson in changes in both white and grey matter; while Lepelletier thought to have discovered a peripheral neuritis in these cases. The most exact observation of the nervous system of patients dying of tetanus, as well as of animals in whom the disease has been produced, do not reveal any changes, either in the central nervous system or in the peripheral. Nevertheless the whole course of the disease indicates a slow spread along the course of these nerves. The poison, whatever it is, probably reproducing itself in nerve substance spreads slowly toward the spinal cord, there to manifest its strongest a tivities. Elevation of temperature is by no means constant in experimental animals, it is seldom manifested. The exaggerated frequency of pulse is ascribed to a paralysis of the vagus.

On the other hand, the humoral theory has had its defenders, who have found plenty of facts upon which to base their views. According to these the alteration of the blood, which they have considered the exciting cause of tetanus, has been compared to poisons with various alkaloids, many of which are known to exert a selective influence on various organs or tissues. Defended especially in the past by Simpson and Travers, and more recently by Roser and Billroth, it supposes a specific toxæmia of the system, the unknown poison exerting a selective influence upon the nervous system. Others have regarded it as a toxæmia, due to poison generated directly in the wound, or to an autochthonous septicæmia, due to a sudden suppression of the functions of the skin, and the failure to eliminate its excretory products. The poison was supposed to be a chemical one, formed in the wound or near it, and thence absorbed into the blood. If this hypothesis were true we should have an evolution of the disease analogous to that of purulent inflammation. Quite recently, and in accordance with the tenets of the germ theory, the idea of a purely chemical poison has been abandoned, and the chief role assigned to micro-organisms. Before the parasitic nature of the disease had been carefully recognized, Lister furnished a comparative proof of the truth of this hypothesis by showing how in six years under the antiseptic method, he had met with but two cases of tetanus, and these in wounds already septic.

Others yet have charged it with being distinctly a zymotic disease, which view had much in its favor, except the fact that until recently inoculation experiments had failed. Of course while each particular hypothesis under both the above headings had more or less in its favor there were objections which were fatal to each except to the last. For this last, namely that of zymosis, there were many corroborative facts, such as the statistics from the Dublin Lying-in Hospital, where there was at one time an epidemic of tetanus neonatorum; the mortality rate within the first fortnight being 17%, which was reduced to 5% after a better ventilation was established.

It has remained, however, for living observers, working within the past decade, to establish clearly the parasitic nature of this dread disease, and to isolate and investigate the organisms by which it is produced. In 1884 Carle and Rattone inoculated rabbits with an emulsion formed by macerating in distilled water a fragment of skin taken from a subject dying of lockjaw. Their results were positive. From them they concluded tetanus to be an infectious disease, but they could neither see nor cultivate the micro-organism which caused it.

The mere establishment of this fact was a very distinct advance in our knowledge of the natural history of the disease, and though some of their statements with regard to the biology of the micro-organisms which cause it, are hardly to be accepted, we, nevertheless, owe the above demonstration to them. During the year following Nicolaier demonstrated that in the ordinary soil of our gardens and streets there are bacteria which, when introduced under the integument of mice, guinea-pigs and rabbits, produce a typical tetanus with fatal termination. Inoculations made with dirt from the streets of Berlin, Leipsic and Wiesbaden gave the same results. Soon after this Rosenbach demonstrated to the German Congress of Surgeons (in 1886) that the same bacillus which Nicolaier described appeared in human tetanus, and soon after this his observations were confirmed by numerous observers.

In his communication to the Congress of Surgeons, Rosenbach first called attention to the fact that experiments had been made in a promising direction by Rose, Frickenhaus and by Arloing and Tripier, and that the latter had experimented in 1870 by injecting dogs and rabbits with blood and pus from tetanic patients, and had also vaccinated healthy horses with the blood of those suffering from this disease, but with negative result. He had himself injected into a dog 60° cc. of blood from a patient with tetanus, also without result; while Schültz and Billroth had done virtually the same thing, yet always with negative result. This was now explained by the fact that all these experimenters used dogs, which are known to be refractory to the disease. It was then that Carle and Rattone succeeded as mentioned above. They injected into 21 rabbits an emulsion made from the pus of an acne pustule, from which a fatal tetanus had developed, and they introduced it into the sciatic nerve sheath. Eleven of these animals died of tetanus. They recognized the fact that the pus so injected was swarming with micro-organisms, but had no success with cultivation experiments. It was in 1886 that Rosenbach made his first inoculation experiments by introducing a small piece of skin from the neighborhood of a wound of a patient dying of tetanus underneath the skin of guinea pigs and saw tetanus develop in each animal within a few hours. Similar experiments with skin from a part at some distance from the poisonous wound had no result. It was evident, therefore, that inoculation succeeded only with material taken directly from the infected spot. He succeeded also in transmitting the disease from animal to animal. These experiments agreed with those of Nicolaier, who got his material from black earth. Socin, Polaillon and Jeannel imitated him successfully, and Hochsinger and Bonome verified his experiments, as also did Shakespeare, of Philadelphia Lumniczer has multiplied these experiments and made a precise study of the bacillus of which we shall speak very shortly in some detail.

It will be seen from the above statement why writers in the past have with reason spoken of the telluric origin of tetanus. Quite recently in Paris Verneuil has strongly defended what may be called the equine origin of tetanus, according to which the earth which causes such lesions and which contains the tetanogenic germs is especially that which has received the dejections of the horse. Tetanus is known to occur very frequently among grooms and those who care for these animals, and falls from a horse and horse kicks are frequently alleged causes of the disease. (Horse dung seems especially suspicious material). It is least common of all among sailors, but when happening among them occurs almost exclusively on board ships used for the transportation of these animals. Numerous reported instances lend a certain degree of plausibility to these views, and they are entitled to at least respect, if not to complete credence. Within the past few weeks I have been called to attend a lad who was caring for a horse that had developed a typical case of tetanus, but recovered therefrom. Before the horse was well the boy ran through the sole of his boot a rusty nail which projected from the floor of the shed in which this horse was kept. In just one week he developed the symptoms of tetanus and died within forty-eight hours. Of course it would be folly to think that the horse generated the germ or the poison, but the coincidence is certainly striking. All the specially infectious bacteria have their favorite soil; those of typhoid and cholera are found most often in water; those of suppuration about the skin and hair, and it is not difficult to admit at least that the germs of tetanus abound especially around the horse.

It is hardly necessary to detail the minutiæ of Rosenbach's experiments. He found, as has every other observer, that the symptoms proceed in almost every instance from the point or part affected; that if it be in a limb that the poison was first introduced this limb is first involved in spasms, and that the so-called tetanus-hydrophobicus could be produced when the inoculation was made about the head or face. Examining the material with which he inoculated, he found a mixture of numerous forms, staphylococci, streptococci, diplococci, large and small bacilli, with and without spores. As one among these many forms he recognized the bacillus described by Nicolaier, but his best endeavors to make a pure culture of the specific organism failed. He even discovered that it or its spores were not destroyed by a temperature of 100° C. after five minutes exposure, and although by thus heating he killed off all or nearly all of the other organisms, he was still unable to make a pure culture of the one he was after.

It has remained for Kitasato to isolate, to cultivate and to study the organism in all its biological and pathological relations, and while he is not the discoverer of the organism, we owe to him mainly what we now know about it. He first worked with the pus from a patient dying three days after the onset of a typical tetanus, as well as with fragments of the splinter which caused the injury. In this material he found three forms of obligate anærobic bacteria, five facultative anærobic forms, and seven ærobic. The principal difficulty of course was to separate from these the particular organism which he wanted, and he succeeded by a method which those who desire to identify this organism will hereafter have to follow. He placed the mixture upon agar or blood serum, and then kept this in the thermostat at 38°C. for forty-eight hours, during which time the tetanus bacilli were stimulated into a free formation of spores. The culture tubes were then placed in a water bath which was kept at 30°C. for from three-quarters of an hour to an hour. By this heat all the other organisms were destroyed and only the spores of the tetanus bacilli were left active. Inoculations of this into mice provoked the disease as typically as ever. He then planted these spores in gelatine and agar and cultivated them as anærobes in an atmosphere of hydrogen at a temperature of 18° to 20°C. And so by fresh refinements of technique which need hardly to be mentioned here he established that the tetanus bacilli might be cultivated in pure form, and that they grew as obligate anærobes with spore formation, their spores being extraordinarily resistant in the matter of temperature.

They are not necessarily killed by exposure to the air but grow only when the atmosphere is excluded. Under hydrogen they grow luxuriantly; under carbonic dioxide, not at all. The agar or gelatine in which they are planted must be very slightly but positively alkaline. They fluidify the gelatine with very slight formation of gas. If to the gelatine or agar 2% of sugar be added, their growth is more rapid, and it is even more so if to the culture material 0.1% sulphindigotate of sodium be added. They can even be grown in alkaline bouillon if hydrogen be present; they then generate a peculiar odor as if something were burnt. They can be cultivated from one generation to another without losing their virulence and without necessity for frequently passing them through animals. They may be grown on plates under hydrogen, but are ordinarily cultivated along the needle streak which very slowly, if at all, reaches the surface. They grow most rapidly at blood heat, very slowly at 20° C., but below 14° C. they do not grow at all. At blood temperature they form spores within 30 hours.

They have three principal phases of existence, *viz.*, a spore stage, a bacillus stage and a spore-bearing stage.

As grown in gelatine at ordinary temperature, they form separate bacilli, or gather in long threads. Where they form spores at higher temperature the spores are round and met with at one end of each bacillus, so as to give it a peculiar hat-pin or drum-stick shape. It stains best during this shape. They possess a very slight motility, which is better demonstrated on the warm stage Bacilli which contain spores, apparently have no proper motion. They take the ordinary aniline colors well, and may be stained by Gramm's method. The spore formation can be demonstrated to advantage by Ziehl's method of double staining. The bacillus seems to multiply by fission as well as by spores.

It is most interesting and important to know that the spore bacilli when dried by the ordinary method and then kept for some days in an exsiccator over sulphuric acid, and then kept in ordinary atmosphere, preserve for months their virulence, and that their spores were found still acting by Kitasato after having been mixed with earth that had been sterilized in a steam apparatus for 10 hours. Evidently, then, tetanus spores are extremely resistant. Moist heat for an hour does not kill them, and, as Rosenbach had previously found, even five months' exposure to moist heat at 100 did not destroy them. Ten hours' exposure in 5% carbolic acid left them still virulent; only after fifteen hours could they be thus destroyed. So also it took three hours' exposure in a 1% sublimate solution, or thirty minutes in the same solution to which had been added 0.5 of 1% of hydrochloric acid. To other chemicals they are equally resistant.

Kitasato left standing for two days a bouillon culture which he shook up with 10 cc. of chloroform. After the chloroform had been removed he injected several animals with the culture and found it pathogenic as ever, while fresh culture grew luxuriantly. When subcutaneously inoculated, small animals develop tetanic symptoms within twenty-four hours and die usually in less than seventy-two. Pigeons appear somewhat liable to the disease. It is evidently quite unnecessary that any foreign body should be introduced along with the active germs, as would perhaps appear from a study of the well-known features of the disease. Ordinarily there is no local reaction at all, and on a section when a splinter has been used, one finds it embedded in a mass of leucocytes without other disturbance.

It is to be emphasized that the symptoms of tetanus are almost invariably at first local, the muscles being first involved at that part where the inoculation was practiced. It is furthermore noteworthy that by the microscope these organisms are never found at any distance from the wound, and that, moreover, even here they perish within less than twenty-four hours, except as they may be found in the pus. Most careful examinations of the brain, the nerves, the muscles, the viscera and even the blood fail to reveal the slightest trace of them, and inoculations practiced with these tissues or fluids are almost always without results.

It is also of great interest that only tissues from the immediate neighborhood of such a splinter are infectious, and that inoculations with blood, brain, nerves or other organs of the animal have never caused the disease. Possibly in the above fact we may find an explanation of some of the cases above referred to, those of the disease supervening long after the healing of a wound, since the period of incubation in man is known to vary within wide limits.

Such a case has indeed been reported by Renvers from Leydens Clinic. Deep in the sole of the foot was found a splinter of wood an inch long. Inoculations with particles from this splinter succeeded, while those made with tissue only 3 millimetres distant from it produced no disease.

Kitasato trephined animals and then inoculated the dura with a pure culture, but after their death was unable to find the slightest trace of the bacilli in the brain tissues or in the blood; while culture experiments with the same all failed. These statements are somewhat at variance with those made by some earlier experimenters, yet they appear to bear the stamp of certainty, and have been corroborated by many other investigators. In order to demonstrate their action still further Kitasato practiced inoculations as before, which were followed within half an hour to four hours by excision of the inoculated area and cauterization of the wound thus made with the actual cautery. The animals died just as if nothing had interfered with the virulence of the disease.

Repeating these experiments several times, I have myself obtained the same results. Although it has seemed to me as if the onset of the symptoms were somewhat postponed and the progress of the disease somewhat delayed. The rapidity with which all bacilli vanish from all the tissues and juices of the body is perhaps the most astonishing feature of the disease. Presumably they generate a poison whose effects are far-reaching, and this poison has been studied by Kitasato and Weyl, who have very recently published a further communication upon the subject. The conclusions arrived at by Kitasato are briefly as follows:

1. Tetanus is a specific disease.

2. The active agent in producing it is a bacillus which is identical with that described by Nicolaier and later studied by Rosenbach, and now determined to be an anærobic organism.

3. This bacillus is found in the pus from tetanic patients and

animals. It often forms spores in such pus, nevertheless may be frequently met with while free from spores.

4. It is possible to cultivate this bacillus from such pus, and with pure cultures of it to reproduce tetanus in animals.

5. The somewhat contradictory statements of early observers find their explanation in the fact that tetanus is met with in various stages, and that the more quickly the animals die from the disease, the more likely are we to find spores in the bacilli. But these bacilli are, or have been, always present, and from them one can always cultivate spore-bearing decendants.

A consideration of the specific factors involved in tetanus, is inseparable from that of the toxines or ptomaines which they produce. During the period intervening between the time of inoculation and the first symptoms of the disease, there probably occurs a gradual increase in the numbers of the micro-organisms, while there is slowly elaborated an increasing amount of those toxic substances. These are at first eliminated probably by the skin and kidneys as rapidly as formed, but they finally accumulate sufficiently to display their activities, first upon the nervous system, and later by the usual symptoms and signs of the disease as well known. It is corroborative of such view that the administration of full doses of pilocarpine in the early treatment of the disease is followed by benefit. The common treatment of the disease as well denotes the same, since the chloral so often given tends to lessen the recognition of afferent impulses, and the bromides to decrease the force of the motor explosion following. (*Med. News.*)

Since Kitasato published his first formal paper in the *Zeitschrift f. Hygiene*, he and Weyl have made three communications upon the ptomaines or poisons by which the bacilli produce the symptoms of tetanus. As is well known Brieger isolated from cultures of tetanus bacilli a crystalline material which he named tetanin. Working with the hydrochlorate of this alkaloid the above observers demonstrated that it produces in mice spasmodic disturbances, and increased flow of saliva.

Another analogous substance separated from cultures in the same way has been called by Brieger, tetanotoxin. Their experiments with this material produced results which were also analogous, and yet it appears from their work that the dose of either of these alkaloids must be relatively so great that one is forced to the conclusion that the tetanus bacillus in the living organism produces a poison of much greater virulence than either of these yet isolated. They promise further studies and the publication of their results.

The investigations of Dr. Shakespeare, of Philadelphia, also deserve mention here. He was able by placing in contact with the central nervous system of healthy rabbits infusions of the spinal cords of tetanic cases, to speedily produce characteristic symptoms of the disease, while the subcutaneous injection of the same material had no effect. Although during his experiments he failed to discover specific micro-organisms, he nevertheless showed what has been demonstrated in another way by others, that the exclusion of the tetanogenic spores by extirpation of the infected sore, or by amputation of the limb in which it occurs, with distinct failure to arrest the disease, confirm the idea of local activity, combined with the elaboration of poisonous matters circulating in the blood. (*Med. News*, Oct. 25, 1890.)

Among very recent experiments concerning tetanus are those of Babes and Puscariu. (*Centrablt. f. Bakteriol*, VIII. No. 3.)

They worked with cultures received from Kitasato as well as with those which they isolated from horses suffering from the disease. From those animals which died as a result of inoculations, only the bacillus from the point of inoculation could be cultivated, but nothing from the veins, or internal organs, nor from the brain or spinal cord. Nevertheless, mice and rabbits which received small doses of these fluids died from some poisoning without tetanic symptoms.

For purposes of experiment, two mice and two rabbits were inoculated with emulsion of brain tissue from a rabbit dying with tetanus. The former died in four days, the latter in eight, without symptoms of tetanus. In the endeavor to discover or invent a protective injection, these experiments were repeated and the emulsions were made with bouillon in different strengths, but the animals nearly all died.

Babes prepared an albumose out of agar cultures which did not contain peptone, whose watery solution was passed several times through a Chamberland filter. This substance sometimes, but not always, produced tetanic symptoms with cramps and paralysis, and fatal results after varying lengths of time.

Tizzoni, Cattani and Baquis have investigated three cases of tetanus, from which they isolated five different forms of bacteria, of which two only were pathogenic. The first of these seems to be identical with that described by Kitasato. The second was recovered from the blood and spleen of an animal dying after subcutaneous injection of specific pus.

It was also a bacillus smaller than the other, having involution forms. and producing spores. It also showed itself to be anærobic. After subcutaneous injection, typical tetanus was produced in most of the smaller animals. These authors were not able to deny, however, that this organism might not be identical with Kitasato's.

They claim that both of these bacilli lose somewhat of their virulent power with time and peculiarity of culture medium. They, like Kitasato, found no protection from excising the point of inoculation. (*Zeigler's Beiträge*, vii, 4.)

A recognition of the minute causes of tetanus raises the question as to what can be done for the disease. Evidently the bacilli themselves remain at the point where first introduced, while the poison which they produce circulates. Numerous observations seem to prove that this poison can be antidoted by reasonably strong solutions of various antiseptics; 5% carbolic solution, or 1% of nitrate of silver, or bichloride of mercury destroy the germs in the culture tubes; so also does exposure to steam for five minutes. The German writers seem to have confidence in iodoform when packed into the wound. The anærobic organisms, to which these bacilli belong, have a powerful reducing action, and are therefore capable of splitting up iodoform and of producing iodine in pure or nascent condition. In experiments upon animals, 10% solutions of iodoform in ether applied to the point of inoculation within an hour afterward have sufficed to prevent the development of the disease, but all experiments go to prove that whatever is done must be done within a very short time after the inoculation. The uselessness of amputation in well marked cases is very plain from the above experiments, as well as of any other destructive or mutilating operation. The method by incision recommended by Bilguer, by which air was freely admitted to the tissues, has in it something to recommend itself. Of course the very earliest possible removal of the foreign body should be effected. Military experiences show that recovery has sometimes followed the removal of the irritating substance. Isolation, nutrition and stimulation, with such drugs as may control symptoms, sum up the internal treatment of these cases.

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LECTURE VII.

SURGICAL DISEASES OF MICROBIC ORIGIN.

SYLLABUS.—*Actinomycosis:* History. Description of the disease, and of the fungus. Actinomycosis in man. Paths of infection.

Anthrax: History. Sources of infection. Bacillus anthracis; its characteristics; intensification and diminution of its virulence.

Malignant Œdema: Gangrenous emphysema. Description of the disease. Anatomical characteristics. Description of its bacillus; biological peculiarities. Immunity enjoyed by certain animals.

Rauschbrand: Symptomatic anthrax. Strong resemblance to malignant œdema; essential differences. Description of its bacilli.

Glanders or Farcy: Brief reference to its infectious organism; the bacillus mallei. Difficulties of diagnosis.

ACTINOMYCOSIS.

UNDER one name or another the peculiar manifestations now known to be the result of the condition termed actinomycosis have been recognized in nearly all civilized countries, and have been noticed especially about the head and neck of domestic animals, particularly cattle. The large variety of names given to these lesions constitutes the best indication of the fact that their etiology was unknown. During the past thirty or forty years they have been more and more carefully studied by veterinarians. In England, for instance, as early as 1833 a peculiar swelling met with in cattle, and known locally as *clyers*, had been somewhat carefully studied by Professor Dick. He dissected several animals which presented these tumors in the parts about the throat, and described them as having a somewhat malignant character, and corresponding to what were usually called "medullary carcinomatous tumors." He noticed also that sometimes abscesses developed, and that when these were laid open healing frequently followed, and that in other cases the open sores remained indolent for a time and then increased until they interrupted respiration by their bulk, and prevented deglutition. In 1841 he made a further report on the same subject, describing now the mouth and throat of a cow in which there was a distinctive tumor, and he spoke of it as a mass of fungus flesh, while a part of the jaw was decayed and absorbed. This time he stated that the disease was not unknown in cattle and that it was well-known as attacking the jaws in human beings; that by surgeons it was denominated osteo-sarcoma of the maxillary bones, and he added that the remote cause seemed to be a scrofulous diathesis, while the existing cause was commonly disease of the molar teeth, or some accidental injury. In 1843 a Mr. Relph described in *The Veterinarian* a "kind of indurated tumor" which he met with in his practice oftener than anything except the common wens. He spoke also of its ulceration and extension until at length animals sank and died of "atrophy or phthisis pulmonarius." He spoke also of a section of one of these tumors as "mostly displaying several abscesses with matter varying in consistency, and often very fetid, enclosed in what seemed to be fibro-cartilaginous cysts." Also, again, of the implication of the nasal sinuses and involvement of the orbital cavity, where bone was being removed and matter deposited, and also that the tongue was much enlarged and ulcerated. In 1845 Professor Simmonds spoke of the diseased condition as an affection termed *scirrhus tongue*, and one frequently found associated with maladies essentially different. Under this term, scirrhus tongue, it was commonly described until quite recently. In 1864 a case was fully described in the *Ed. Vet. Rev.* under the title of "Cancer of the Tongue in an Ox." On the continent also this disease had been everywhere misunderstood. It had been frequently regarded as a tubercular infection or mistaken for a simple chronic glossitis; while the continental languages were full of common names for it, and veterinarians spoke of it as osteosarcoma, bone cancer, spina ventosa, etc. In 1876 Bollinger presented to the Society for Morphology and Philosophy at Munich a learned paper on the subject, with a demonstration of microscopical and gross specimens. He pointed out that these tumors consisted of several centres of growth bound together by connective tissue, whose cut surfaces presented yellowish white suppurative foci, or at times a spongy texture, owing to the formation of minute cavities in a fibrinous crust, which contained a thick, yellow, caseous pulp. The microscope revealed a structure something like that of sarcoma, while the expressed juice contained, among other materials, small granular bodies which had a mulberry like appearance, and were sometimes encrusted with chalky matter. He had discovered that these latter bodies were true fungi, and he further maintained from the constancy of their appearance and they were not accidental but had a pathological significance. These also he had met with in old museum specimens.

Bollinger had observed this remarkable formation not only in the upper and lower jaws, but also in the tongue, in which latter organ, when recent, it much resembled the condition produced by tuberculosis. If these nodules were situated on the surface of the tongue they rapidly led to the formation of ulcers. It was possible also for an interstitial glossitis to occur, which, in spite of partial atrophy of muscle fibres, led to enlargement and peculiar hardness of the tongue, from which the infection gained, in German, its popular name *holz-zunge*, or wooden-tongue. On continuing his researches further, he discovered the same fungus in tumors which occurred in the pharynx, larynx and stomach. He even described this fungus in a case of so-called fibroid of the second stomach of a cow, and in a form of apparent tubercular ulceration of the intestines. He submitted the fungus to the botanist Harz, who described it and assigned it to a temporary position. Cultivation experiments and inoculation of the tongue of a calf with liquid containing the organism, all failed. Its name was given by Harz. Bollinger's paper was published in 1877 and attracted wide-spread attention, and brought out the claim from Perroncito and Rivolta that they had already discovered the same organism in 1863 and 1868 respectively. It is very probable that Hahn, of Munich, met with the fungus in 1870, since he states that in a case of wooden-tongue he found characteristic structures, which he described provisionally as a species of mould fungus, but Bollinger was certainly the first to study the organism systematically, and to throw an entirely new light upon the pathology of the infection, and his researches were corroborated by Siedamgrotzky, by Johne and by Ponfick; and so by one observer and another on the continent, and later in Great Britain, the pathological identity of the various lesions included under so many different names was established, and the names of Boström and Israel, of Axe and Crookshank, and of many others in addition to those already named, have become inseparable from the subject itself. During the year 1858 a most important memoir was sent to the agricultural department of the Privy Council by Professor Crookshank, of King's College, which was published in the annual report of that department for that year. It is a most elaborate document, extensively illustrated, and prepared with the greatest care, and to it the writer is largely indebted. One of the things for which we are especially indebted to Professor Crookshank in this matter is the establishment of the fact that many of the lesions in animals which had before been considered due to tuberculosis, are in reality manifestations of actinomycotic disease, a beautiful proof of which that gentleman has kindly afforded me in his own laboratory, while in the document referred to it is amply evidenced by illustration. Altogether we regard this report pertaining to animals and men as well, and comprising 80 pages, as presenting perhaps the best summary of the subject which we have.

The disease, as Crookshank and others succinctly state, belongs to the class of infective granulomata. It has an irritative, inflammatory action, brought about by the presence of a special irritant, a microphyte, and consists of a collection of round, epitheloid, lymphoid and giant cells, enclosed within a fibrous reticulum. There are thus constituted nodular tumors of various sizes. Sometimes these attain large dimensions, at other times they break down early and suppurate. While it appears, as seen in a former lecture, that the actinomycotic fungus may by itself produce pus, it is nevertheless equally true that suppuration in actinomycotic tumors is commonly due to a secondary infection by the ordinary pyogenic organisms. Calcification takes place sometimes in the fungus tufts, and altogether the actinomycotic nodule so closely resembles the tubercular in its minute character that it constitutes almost a mimicry of the latter. Its most characteristic manifestation in cattle is betokened by the popular name most frequently given to it, namely, *lumpy jaw.* It is especially prevalent in river valleys and marshes, and on land reclaimed from the sea, and in animals appears to occur more frequently in the winter, and more often in the young than in the old. There is strong reason for believing that the fungus gains access to the system through wounds or ulceration of the mucous membrane, or through carious tissue. It has been pointed out that the common occurrence of the disease at the time of second dentition may be due to the wounds produced during the shedding of the teeth. It is supposed, also, that thistles and frozen roots, by wounding the parts, may afford a path of entrance. Discharges from infected animals are thus infectious, and cow sheds and pastures, drinking troughs and fodder may be easily contaminated.

The fungus itself may be detected with the naked eye in the discharge of an actinomycotic ulcer, or in the scraping from a cut surface or growth. Its tufts vary in size from that of a grain of sand to that of a pin's head. If the material contained be spread out on a slide and examined against a dark back-ground, these granules appear white or yellow-white in color, but if examined in transmitted light they appear distinctly brownish. If they are pressed down with a cover glass they readily flatten out, while possibly a distinct gritty sensation is transmitted to the finger, owing to the presence of calcareous matter. With a low power the fungus will be recognized in the form of irregular patches scattered over the field, which might at first be mistaken for granular debris, but which on more exact examination will be observed to have a characteristic appearance. With a higher power masses will be seen which look like a rosette of clubs, or which have here and there throughout the margin a club-shaped projection. Of course with these bodies, pus cells and other granules will be found. By pressing upon the cover the rosette is broken up and then the club forms are recognized singly or in twos, or in the shape of fan-shaped segments. The presence of calcium salts may be readily demonstrated by the acids which dissolve them; by which the clubs are not affected. The club-shaped masses are not affected by ether, nor by potassium hydrate, which shows that they are not fat crystals. By teasing the little cluster we may break it up into its club-like elements, and these may be examined with still higher powers. When these grains are placed in water and teased out, the center portion seems to be composed of a structureless core. When the organism is removed from the disease in man, it appears to present minute and delicate filaments which are not present in those removed from animals.

Actinomyces were generally regarded as belonging to the higher micro-fungi until Boström put forward a new theory. By Harz and Johne the club-shaped prolongations were considered to be conidia and the threads to be hyphæ. Boström on the other hand thought that the clubs should not be regarded as conidia, but the result of a pathological stage of the threads, and he considered that the calcification which occurs in them supports his view. If this were the case, cultivations could not be successfully made from the clubs, but must be made from fungi containing threads. He made cultures from five animal cases and one human, and obtained a similar result from all. The fungi were isolated from pus with sterilized needles, were placed in liquified gelatine, in which they were teased out, and the gelatine then spread on glass plates. In a few days the growth became visible. The fungi were then isolated from the plates, crushed between sterilized glass slides, and planted on the surface of nutrient agar and blood serum. In this way pure cultivations were obtained, and the culture which I show you herewith is made from a descendant of one of his original cultures. It grows in a peculiar way, with a finely granular whitish appearance; after a few days small yellowish red spots appear in the center, increase in size for a week or so, and then become confluent, while the margin is also dotted with similar spots. Isolated colonies as they appear have a yellowish red center with a grayish margin. Boström states that the actinomycis is not one of the mould fungi, and its central threads do not constitute a mycelium. He was inclined to regard it as a branched cladothrix.

Johne and Ponfick made a careful series of experiments to prove that actinomycosis is transmissible from animal to animal. Inoculation experiments, whether subcutaneous or intra-peritoneal, as well as intra-veinous injection, were successful. Feeding experiments gave negative results. It appears from their researches that rabbits and dogs possess a marked immunity, while the cow is, perhaps, the most susceptible of all animals.

We are naturally most interested in this disease as it appears in man. In 1878 Israel published the drawings made in 1845 by Langenbeck, then in Kiel, of a case of vertebral caries, in the pus from which peculiar bodies were observed. There can be but little doubt that these structures were the fungi of actinomycosis. But the first published observations will be found in Lebert's large work on pathological anatomy, described in the text and figured in the atlas. In 1848 Lebert received some pus of great consistency which had been obtained from an abscess in the thoracic wall in an elderly man. The patient had been thought to have a cancerous pulmonary affection. The pus contained a very considerable quantity of minute spherical beads, which could be crushed between two strips of glass, and in which, under a low power, radiating wedge-shaped bodies were found. Lebert tested these bodies most carefully with chemical reagents, and had in mind the possible existence of some helminthic débris of which these bodies might be hooklets, but he sought in vain for the common parasites. Actinomycotic pus was later described and figured by Robin, but the first adequate description of the disease in man was made by Israel, who was soon followed by

Ponfick. By these two writers the various cases which had been observed up to that date were collected and described and the disease classified according to the seat of invasion. Up to the time of Crookshank's report he had collected about one hundred and thirty human cases, and from those as well as from the work of Israel, the following description is largely drawn.

Invasion by the mouth and pharynx.—The fungus may gain access through carious teeth or wounds or fistulæ of the jaw, and possibly by the pharynx and tonsils; it attacks the lower jaw most frequently. The consequent tumor is found in close connection with the bone, and just beneath the jaw or in front of the trachea. Actinomycotic tumors in this region appear to correspond very closely with the *clyers* already described in cattle. As in cattle, they may discharge through the skin, although they differ in their tendency to form burrowing abscesses instead of recognizable tumors. The upper jaw is much less frequently attacked than the lower. The progress of the disease is usually slow, and there is a tendency to the deep seated parts becoming involved ; while when the lower jaw is attacked the tumors tend to approach the surface. In other cases the disease has been described as extending from the alveolar process to the temporal bone or the base of the skull, destroying these bones and even reaching the brain. In yet other cases, it has extended along the spinal column, implicating the vertebræ and traveling and pointing in various directions. The first cases of actinomycosis hominis which were observed in this country were connected with the jaw, and were described by Dr. Murphy, of Chicago. Both recovered after thorough curetting. In one recorded case the disease existed for seven years, was localized in the bronchi (bronchitis actinomycotica) and did not extend into the lungs. The sputum was examined and contained the characteristic fungus. If the fungi be inhaled they pass into the lungs and produce proliferation of round cells, which undergo fatty degeneration. The resulting patches of peri-bronchitis or pneumonia become yellowish white. Suppuration and hæmorrhage follow, and the resulting small cavities contain pus cells, fat granules, blood and fungi ; ultimately a dense layer of connective tissue is formed around the cavities, which are lined with granulation tissue containing the characteristic fungus. The symptoms are usually obscure, but the specific organism may be found in the sputum, and is in fact often recognizable with the naked eye. The apices of the lungs are not, as a rule, affected. There is considerable resemblance in clinical course to chronic or fibroid phthisis. In the second stage the symptoms are more severe. The disease spreads to neighboring parts and often pleurisy supervenes. The disease has been known to descend behind the diaphragm and point as a psoas or lumbar abscess; or to perforate the diaphragm, reach the abdominal cavity, and there set up peritonitis or sub-phrenic abscess. The disease may also extend forward in the direction of the pericardium and anterior mediastinum. In the third stage the disease comes to the surface, either over the chest or in the neighborhood of the vertebræ; a livid swelling appears from which no fluid escapes on puncture, but which works its way to the surface, and then discharges the mucopurulent fluid, in which the fungi are easily recognized.

Invasion by the digestive tract.—Chiari has published a case dying from general marasmus, after two years' illness, at the age of 34. The mucous membrane of the intestines was completely covered with whitish patches closely adherent to the adjacent tissues. In this case the teeth were carious. In such cases generally small nodules about the size of a pea may be found in the sub-mucous tissue and in the mucosa itself, they soften and form ulcers with determined edges, their bases reaching the deepest layer. These may undergo cicatrization, but generally ulceration extends through the peritoneum to the abdominal cavity, and we have perforation of the bladder or the intestines, or perhaps of the abdominal wall. Symptoms are absent or not characteristic. The fungus may be found in the evacuations or by exploratory puncture.

Besides such cases as the above, which can be easily classified, there are a number of recorded cases presenting varied symptoms and anatomical relations in which the path of infection has not been determined. It may be said in common of all cases, however, that no matter where the lesions may be situated, the discharges therefrom present always typical characteristics.

The first case of actinomycosis in man met with in Great Britain was described by Dr. Harley in 1885, the patient being an inmate of St. Thomas Hospital. The next two cases were recognized by Mr. Shattock, who published them in the "Pathological Transactions" in 1884 and 1885. Numerous other cases are described in English journals, and it is a matter of interest to know that numerous specimens which had long been deposited in museums, that of the College of Surgeons, for instance, and had been described under other names, were found to be genuine cases of actinomycosis. It is worth while also to know that since the introduction of Gram's method of staining, a distinctive advance in the recognition of the organism has been made, since by this method, combined with staining by orange rubin, as pointed out by Crookshank, the threads are stained blue and the clubs crimson, while in the younger clubs the protoplasm of the thread can be traced into their interior. Evidently, then, the best method of preparation is Gram's stain followed by eosin or orange rubin. Inasmuch as Gram's method had not been applied by either Israel or Koch in the earlier part of their studies of this disease, it is not strange that most of their writings have failed in the complete description of the organism which the later reporters have given.

So far as the source of the disease in man is known, many interesting observations have been made. Two cases have been recorded in support of a theory of direct infection from the cow. One of these occurred in a man who had the care of animals, some of which were diseased, the other in a man who had charge of cows, one of which had a tumor of the jaw, which tumor he had opened. On the other hand Moosbrugger found that out of seventy-five cases, fifty-four were in men, nineteen in women and two in young girls. In eleven of these the occupation was not stated, in thirty-three their occupations did not bring them into contact with diseased animals. Only ten of his cases occurred among farmers, peasants and farm laborers, and only one of these ten had been brought into contact with diseased animals. Of the twenty-one women there were only four peasants and none of them had been taking care of diseased animals. Infection by the flesh of diseased animals has also been discussed, but there is no evidence of prevalence of the disease among butchers, who would be particularly liable to it if flesh were a source of infection. Moreover the chances of infection from this source are minimized by the flesh being almost always cooked. To be sure the disease occurs also in pigs, and pork is often eaten in an uncooked state; and Israel has pointed out that the disease has never been known to occur among strict Jews. Evidence seems to point to the origin of the disease among the cereal foods. This view is supported by observations with reference to the part played by cereals in inducing the disease in cattle, an origin well known, and it gains additional support from a case described by Soltman where the disease resulted from swallowing an awn of barley. This was accidentally swallowed by a boy of 11, who became very ill and suffered great pain behind the sternum extending to the back. An abscess formed, covering an area extending over this inter-costal space, and when opened the awn of barley was found in the evacuated pus, but pain continued and fresh deposits occurred, and when the boy was taken to the hospital, the specific fungus was detected.

As Crookshank states, it has not been possible to trace every step in the life history of many of the basidiomycetes; but if we regard the ray fungus in the light of what is known to occur in many species, this life history may be explained about as he explains it, thus: The spores sprout into hyphæ, and these form fine threads which branch irregularly and sometimes dichotomously; the extremities of the branches develope the club-shaped bodies; these are so closely packed together that a more or less globular body is formed with a central core composed of a dense mycelium. By Gram's method, these threads can be differentiated into an external sheath with protoplasmic contents. The club-shaped body appears to be externally mucilaginous, while internally it is continuous with the protoplasm of the thread. In all probability the clubs represent organisms of fructification. If this be correct the protoplasm in the interior of the club may possibly undergo changes leading to spore formation, the spores being ultimately set free. At other times the clubs themselves seem to sprout, and the sprouting forms to suggest teleuto-spores. In whatever way formed, there is but little doubt that spores are set free in the vicinity of a rosette, and give rise to fresh individuals, and that spores and young fungi are taken up by wandering cells, by which they are conveyed to a distance where they reproduce their kind.

At the Congress of German Surgeons in 1890, Israel and Wolff made an important communication on ray fungi, and their successful cultivation outside of the animal organism, and their successful implantation of such cultures upon the animal. In this a claim was made that they were the first to succeed in cultivating the actinomycosis and implanting it, which claim would appear to be unjustifiable, since, so far as I can learn, Boström anticipated them in this work by several years. Still their remarks and their demonstrations were most entertaining, and the question of priority is one of minor importance. That they did succeed is established, and the fact that it is possible to produce an artificial actinomycotic disease in animals is established beyond a doubt.

ANTHRAX.

This goes also by the name of *milzbrand* in German, *charbon* in French, and is known in common parlance as *malignant pustule*, *woolsorter's disease*, and often as *carbuncle.* The latter, term however, is unfortunate and is liable to misuse. The common carbuncle is simply a phlegmonous process accompanied with a large amount of tissue necrosis, produced probably by common pyogenic or perhaps saprogenic forms, and although I have once found in the blood taken from a large typical carbuncle of this character, on the back of the neck, bacilli much resembling in form and appearance those of true anthrax, I regard their presence there as accidental and do not think that I had to deal with any specific form. On the other hand the malignant pustule of animals has about it much that reminds one of carbuncle in man. In animals the disease has been known for centuries, although it remained for observers who are still living to demonstrate the specific organism by which it produces contagion. Various descriptions of the disease in man occurred during the latter part of the previous century, and its primary existence in man was apparently first claimed by Boyle in 1800.

Of the specific bacillus which is the prime cause of this disease it is hardly necessary to speak, except to remind you of its peculiar resistibility to influences which are destructive to most micro-organisms, and of the little trouble with which it can be utilized in the laboratory because it is so easily cultivated, so readily inoculated and because of the ease with which it can be demonstrated in the circulation and the tissues. In scarcely any organism can the development of spores be better watched, and except for the dangers attending carelessness in handling, it is a most satisfactory organism with which to work. There is this peculiarity attending it, that in the bodies of living animals these organisms multiply solely by segmentation, never producing spores while their host is still alive. Their spores are produced only in dead media, with favoring temperature. whose limits are 15 and 45C. According to Koch, the disease spreads among animals by germinating spores which cling to grasses and plants in moist localities, and which are taken in with the food and cause the intestines to become the first seat of infection.

When the disease occurs in man it is almost invariably contracted from the carcass of some infected animal, or the products of the same. The term wool sorter's disease is most significant, as showing, perhaps, the most common source of contagion. So long as the skin remains intact it is protected; the slightest abrasion may serve as port of entry for the germs; even the mucous membranes may be infected either by bacilli or their spores. It is said that these latter are so minute that they may reach the circulation through a healthy mucous membrane; and the disease is often conveyed by the bites of mosquitoes or flies which have fed on infected animals.

The micro-organism of anthrax has been studied more than any other save that of tubercle, and some remarkable effects have been produced by experiments with it in the direction both of intensification and attenuation. By cultivating it in bouillon for three weeks its infectious power is diminished, and animals inoculated with it are in large measure protected against the disease. Still further immunity is obtained by a second inoculation with material not quite so weak. Animals thus treated a second time are protected for some time against the most virulent form of the disease. Woolbridge secured immunity by cultivating the bacillus in an alkaline solution at blood temperature for two days; he then filtered the fluid and injected a small quantity of it into the subcutaneous tissue of rabbits, which remained well and resisted injection of most virulent blood. Some of Koch's pupils have isolated an albuminose from anthrax cultures, which renders small animals immune against the most virulent cultures. This was prepared by a precipitation with absolute alcohol, and was separated from all possible ptomaines by the same medium. It was then redissolved and filtered through the Chamberland filter. Animals which were inoculated with virulent anthrax spores and injected at the same time with this albuminose recovered. Ten mice each received one-millionth of their body weight of anthrax albuminose, and anthrax culture at the same time. Of these only three died. Vaccination after this fashion has been carried on extensively, among sheep, by Pasteur and his pupils or assistants, and a large degree of success has been attained, although by no means all the animals have survived; and the spread of the disease in France has thus been largely checked.

On the other hand the virulence of the bacillus is increased by successive inoculations in susceptible animals, although it is decreased by passing through different species of animals. It has also been found that attenuated virus will become more virulent by adding certain substances, for instance, a very small proportion of lactic acid; one five-hundredth part of this acid, added to a mixture and allowed to stand for twenty-four hours, doubles its virulence. If to this mixture a little fermentescible sugar is added, in another day the virulence becomes extreme, and frogs, which inoculated with ordinary virus live from forty to fifty hours, when vaccinated with this intensified material die in from twelve to fifteen.

When the spores of anthrax are inhaled, we have primary bronchial and pulmonary lesions. When ingested with infected food or water, we have primary intestinal anthrax. Secondary specific bronchitis, pneumonia or enteritis are met with in almost all cases, if time enough elapse. When the spores are inhaled they lodge upon the mucous membrane, are quickly converted into bacilli, and then insinuate themselves between the cells and into the capillary vessels. In the intestine they affect the mesenteric side of the bowel, lodging usually upon the more prominent ridges of mucous membrane.

Bollinger classified lesions in man as follows:

1. Anthrax acutissimus or apoplectiformis.
2. Anthrax acutis.
3. Anthrax sub-acutis.

External infection is usually produced through a small wound or abrasion. If the microbe meets with sufficient resistance at the point of invasion, its activity is largely or entirely localized; if not, it enters the blood-vessels, causes general and fatal infection. The so-called malignant pustule is in large measure determined by anatomical structure, which needs be dense and vascular. This quickly forms a phlegmonous necrotic area, resembling in most respects a common carbuncle. If, however, a vein be opened in the infectious process, general infection is not prevented by formation of thrombi. There is another form of this disease known as *anthrax œdema* which occurs in parts composed of loose connective tissue with meagre blood supply, conditions met with about the eyelids and neck. Here the disease appears as a flat infiltration without well-defined borders, the skin being little or not at all discolored, while an œdema spreads rapidly in all directions. General infection occurs more easily from this form than from the other, although spontaneous cure is possible. So long as infection remains local, there are few general symptoms; but with general infection we have signs of rapid and overwhelming sepsis.

In man this inflammation seldom terminates in suppuration without secondary infection by pyogenic cocci, which, however, may easily occur. Bollinger believes that in his first and most virulent form the rapid growth of the bacillus in the vessels brings about a sudden diminution of oxygen, and a surplus of carbonic di-oxide with consequent asphyxia; but experiments fail to confirm this view. Another hypothesis is that death results from mechanical causes, that is, obstruction in the blood vessels from large numbers of bacilli; but this is not borne out by facts. The view that the essential toxic agent is some chemical substance generated by the bacilli has much more to commend it. Bollinger and others have succeeded in separating from anthrax cultures an alkaline substance or alkaloid having profoundly toxic effects, and, without rehearsing the various experiments which have been made, there is every reason to believe that the fatal termination from anthrax is largely due to the action of toxic ptomaines or of toxines produced by the bacilli as products of their growth.

Woodhead and Wood have experimented with a combination of anthrax and bacillus pyocyaneus, and they have found that anthrax bacilli which would kill a control animal in three days required nearly three times as long when twice a day a sterilized pyocyaneus culture was injected underneath the skin. They are of the opinion that this effect is not produced through phagocytosis, but through an antagonism of poison. since outside of a body the anthrax bacillus grows very well in a culture of green pus.

MALIGNANT ŒDEMA.

The disease known as malignant œdema, to whose parasitic nature especially I desire now to call attention, has been recognized for some time under such names as *gangrène foudroyante* (Maisonneuve), *gangrène gazeuse, acute purulent œdema* (Pirogoff), *septicémie suraiguë and septicemie gangrèneuse;* also as *gangrenous emphysema.* The term under which we speak of it, namely, malignant œdema, was given it by Koch, who identified its parasite. It is one of the most dangerous forms of gangrenous inflammation, which occurs sometimes after serious bone injuries, and sometimes after so trifling lesions as those inflicted by dirty pointed instruments, or even the stings of insects.

The characteristic feature of the disease is the rapidity of its spread, the septic character of the inflammatory product, and the speedy destruction of the tissue involved, with the formation of gas. A dirty brownish, reddish skin, mottled with blue, whose veins are filled with stagnant blood, covers the affected areas. The underlying tissues are sodden with fluid and distended with gaseous products of decomposition, so that the finger feels a fine crepitus, as is common in subcutaneous emphysema. From the wound, if there be one, flows a thin, foul smelling secretion, which may also be expressed from the deeper layers. That the neighboring lymph spaces, vessels and glands are actively participating in the transmission of septic products is evident from the enormous swelling which the latter present, and from the general condition of the patient. The rapid elevation of temperature, with but trifling remission, remains constant until shortly before death. The tongue early becomes dry, cleaves to the palate, its surface covered with thick foul fur. Consciousness is early lost and patients become peculiarly apathetic, complaining only of pain and burning thirst. Sometimes they are delirious instead of apathetic; coma, incontinence, frequent and superficial breathing and dilatation of the pupil are the precursors of death, which may occur in from fifteen to thirty hours. In rare cases life has been saved by the introduction of most vigorous stimulants and sustaining measures. After death the cadaver bloats quickly and putrefaction goes on with singular rapidity. At the seat of the lesion muscles and tendons will be found macerated, the bone denuded, surrounded by a putrid fluid, and the entire region presenting a notable swelling and infiltration of the soft parts with reddish fluid and stinking gases. It is in this fluid that one finds the largest number of microorganisms. The overlying skin will be stretched and superficial blebs or blisters may typify the intensity of the process. The water-logged muscles are friable, the veins are engorged with black and decomposed blood and broken down thrombi, and in the heart and large vessels will be found at the same time putrid liquid and gas, to the presence of which latter the early and sudden death has been with much propriety attributed, since it may cause death in the same way as does air embolism. The viscera are congested and œdematous, and present hæmorrhagic infarcts.

This terrible complication supervenes ordinarily within from eight hours to six days after injury. Its approach has been sometimes betokened by depression and sadness and by chills. Frequently excessive pain and sense of constriction are complained of around the wound. Sometimes the skin has assumed such a peculiar appearance as to justify the term bronze erysipelas, given it by Velpeau (*érysipèle bronze*). The gaseous products of putrefaction, crepitating under the finger, rapidly infiltrate the wound, distend the cellular tissue and extend along the vessels to the glands. The injured spot instead of suppurating simply dies and emits an abundant sanious liquid.

It remained for Koch, in 1882, to demonstrate upon the smaller animals a pathogenic bacillus which he had recognized and cultivated, and which also Pasteur had described under the name *vibrion septique*. This organism is a bacillus much resembling in form and size that of anthrax. Nevertheless it has certain important points of difference by which it can be easily recognized. It is somewhat smaller than the bacillus of anthrax, has rounded ends, and is joined in threads after a fashion quite different. It possesses the property of spontaneous motion, which anthrax bacilli do not possess. The most important morphological difference, however, is in spore formation, since when these bacilli produce spores they enlarge in the middle or at one end, in which enlargement the oval, brilliant and bluish spore is soon developed. Bacilli of malignant œdema take stains just about as do those of anthrax, but they evince much less resistance to Gram's method than do the others; it is in cultures that they show the widest differences.

They do not grow on gelatine plates after the common fashion nor even in needle cultures except when the needle is driven down deeply, almost to the bottom of the gelatine tube, and then they grow along the lower portion of the needle track. Thus it will be seen that these bacilli belong to the most marked form of anærobic organisms with which we are acquainted, and that they grow only when oxygen is entirely excluded. Pasteur was the first to succeed in cultivating them in this medium with the exclusion of air. Gaffky invented a method of cultivation by introducing into the interior of a cooked potato a fragment of tissue in which they were growing. Hesse later taught how to make pure cultures of them in agar and gelatine, by simply sinking fragments of infected tissue into the depths of the tubes, while Flugge, by resorting to cultures in vacuo, succeeded in attaining the same object.

The bacilli of malignant œdema grow best in nutrient gelatine to which 1 or 2% of grape sugar has been added. In such a medium the needle streak shows the development of the organisms at first in its lowermost portion by a series of minute varicosities, which consist in the interior of opaque fluidified gelatine, and around the margin of fine radiating streaks. In their further course the entire lowermost portion of the gelatine liquifies and becomes opaque. In agar they behave in much the same way, save that they do not fluidify the medium. The minute chemistry of these changes is not known. It can hardly be considered a putrefaction since no foul-smelling product is produced. On agar plates where they can be grown in an atmosphere of hydrogen the colonies show very distinctly. Coagulated blood serum is quickly fluidified by them with production of gas. In all media they grow best at body temperature, although even at 18° or 20°C. they show a typical proliferation. According to most authors spores are never formed in the living body, spore formation being apparently a post-mortem phenomenon.

In most respects these bacilli behave as out-spoken saprophytes. Their known habitat is, in fact, the outer world, from which do they only rarely make an incursion into the animal body. They are most commonly met with in the outermost layers of the soil, and garden earth nearly always contains them. Aside from this they may be met with in any kind of soil or dust. The researches of Gaffky seem to make it clear that the bacilli may penetrate from the intestinal canal into the body tissues. The horse seems to manifest the greatest predisposition for the disease, although it may be met with or artificially produced in all domestic animals. A few years ago Brieger and Ehrlich reported an extremely interesting case of malignant œdema following typhoid fever, in which the disease followed a clinically typical course to its fatal termination. Rosenbach later reported two typical cases not connected with typhoid, in which he found the bacilli in question. We must not omit in this place, however, to mention that gangrenous emphysema, more or less resembling the disease under consideration, may be produced by other bacteria, especially the more ordinary putrefactive forms, and that the necrosis or gangrene proper, which is so significant a part of the picture in malignant œdema, is not primarily produced by the specific bacilli, as may be proven by the results of experiment. When a pure culture of these specific bacilli is injected, there is produced a most extensive hæmorrhagic œdema of the subcutaneous cellular tissue without any appearance of putrefactive action; and quite free from gas formation; but when an impure culture is injected, or when garden earth is used for in-inoculation, the distinctive œdema of the previous instance becomes a mixture of emphysemic œdema and gangrene, which latter is, in all probability, due to a mixed infection of the common putrefactive forms, among which, perhaps, may be reckoned the pseudo-œdema bacillus of Liborius.

Experiments on animals seem to indicate that an ordinary cutaneous inoculation is of no effect, nor even is an intra-veinous infection of the organisms. They need to be planted subcutaneously in the areolar tissues in order to produce the typical results. Those which are injected into the blood probably find in the arterial capillaries too much oxygen to permit of their living. The fact that they do not enter through a mere abrasion of the skin is probably the secret of the known immunity of man and beast from this disease, since the earth in which laborers work day after day with abraided hands and feet, and yet with impunity, is the same as that which, introduced beneath the skin of a guinea pig, will quickly determine its death. Nevertheless, the disease is not always fatal, and the larger animals not infrequently recover. Microscopical examination of the tissues from an infected area, supposing the examination to have been made immediately after death, shows that the bacilli are never found inside of the blood-vessels, but mainly in the superficial tissues of the thorax and abdomen, or possibly in the lymphatic spaces of the pleura or of the peritoneum. The blood and tissues of the mouse constitute a possible exception to the above statement. According to certain French investigatiors one attack of this disease confers immunity from subsequent infection, but the opposite view has been taken by others, that one invasion of the disease leaves the system particularly susceptible to others.

Last summer a case was related to me by a Russian physician, Dr. Rekowski, of malignant œdema apparently the result of a hypodermic injection of a solution of morphine. At that time the Doctor was investigating this subject in the laboratory of the Hygienic Institute in Berlin. I have not yet seen any publication of his results, although I know he intended to ascertain the effect of morphia in solution as accelerating or inhibiting the growth of these organisms. At all events such a case as this adds this possible danger to the already formidable list of dangers from injections of solutions not freshly made.

Quite recently Roger has made some very interesting experiments with the bacillus of malignant œdema, and has shown that rabbits possess refractory organisms, but if he introduced at the same time virulent œdema bacilli along with the bacillus prodigiosus, there developed the most characteristic features of œdema, and the animals died inside of twenty-four hours. The œdema bacilli could be recognized in the blood and in the internal organs, the other variety only at the point of inoculation. The œdema bacilli from the first animal were now able to kill the second when inoculated, but when the third was inoculated from the second there was no result. These experiments are convincing that microbes which are not pathogenic for a certain species of animal can be made so when inoculated together with others.

RAUSCHBRAND.

Rauschbrand is a disease quite common among cattle in central Europe, known to the French as *charbon symptomatique*, and to the Italians as *carbonchio sintomatico*, while in Great Britain it is called the *black-leg*. It is a disease very similar in its manifestations to malignant œdema, is well known to be due to an anærobic bacillus, and has so much in common with malignant œdema that I have proposed to speak of it for a moment here, although I have been unable to find in literature any case in which a human being has been attacked with it. A most marked difference between the two forms of trouble is the formation of gas in the diseased tissue, which in the case of malignant œdema is of putrefactive odor; otherwise it might be hard to tell sometimes with which condition we have to deal.

The bacilli of rauschbrand possess many similarities to those of malignant œdema. In form and size there is of course a resemblance, but with minute differences in the manner of spore formation; while the rauschbrand bacilli seem to be in the highest degree anærobic. In their manner of growth there are also trifling yet distinctive differences, and it is found that inside of living tissue spore formation, which apparently takes place only at the end of each organism, occurs with greater freedom. They are also more motile than those of malignant œdema. The most notable differences are observed in different animals in their liability to the two diseases. Cattle are apparently the proper victims of rauschbrand, while they are not subject to malignant œdema. On the other hand swine, dogs, rabbits, fowls and pigeons are but little, if at all, subject to rauschbrand, but succumb very readily to œdema. Horses can be made to react upon artificial inoculation, but appear never to suffer from spontaneous rauschbrand. They are ready victims to the bacilli of malignant œdema. Another significant difference between the organisms is their common habitat. Oedema bacilli seem to be found everywhere in the more superficial layers of earth, whereas rauschbrand seems to be strictly confined to certain localities, although what it is that brings about this state of affairs is not yet known. Again, survival from one attack of rauschbrand, or vaccination with attenuated virus, seems to confer immunity, whereas this is not the case with malignant œdema, but rather there seems to remain an increased susceptibility to the disease.

It was, indeed, a recognition of the former fact, namely, the immunity which one attach of rauschbrand confers, that led Arloing and his co-workers to practice protective inoculation, which now has been very extensively carried out; and it seems to have served a most excellent and useful purpose. It seems to be the general conclusion that rauschbrand bacilli are capable of transmission from mother to fœtus, and that the latter may be affected in this way. The positive proof of this fact which has apparently been furnished is of wide-reaching importance, because if it can occur with one organism, it can undoubtedly with others, and this is a principle which needs to be well established because of its important bearing upon the question of transmission of disease. Within the past year or two there has been apparently a large amount of interest excited in these questions, and a number of workers have devoted a large amount of time and energy to the work, especially in estimating the absolute protective value of preventive inoculation as against this disease, as also in putting an estimate of the money value and giving the whole matter an aspect of national financial importance. The outcome of this work appears to indicate that preventive vaccination offers nearly the same protection against rauschbrand that in another way it offers against small-pox in the human race.

Roger has studied the immunity of rabbits against rauschbrand. It is possible to increase their natural immunity by injecting into their veins daily a number of rauschbrand bacilli. If, after this, rauschbrand bacilli and b. prodigiosus mixed together are injected into the muscles, then the animal shows at most some reaction, from which it soon recovers. Whereas were not the specific bacilli first injected in the veins they would always perish.

From a series of experiments of this kind, suitably varied, Roger comes to the conclusion that the chemical products of the b. prodigiosus do not, as he had at first supposed, alter the tissue at the point of inoculation, but that they act on the entire organism. He obtained the same results with pigeons, which, like rabbits, are refractory to the disease. The susceptibility of rabbits to this disease after the injection of the prodigiosus does not remain long, and they soon become refractory again. He found further that rabbits, which were not affected by intramuscular injection of rauschbrand bacilli, developed the disease when the same were injected into the anterior chamber. From this they died in eighteen to forty hours. The eye is swollen and often contains gas. The entire organ becomes sodden with bloody fluid in which bacilli abound. A similar exudate occurs at the base of the brain. If he injected rabbits in both ways at the same time, *i. e.*, in the anterior chamber and the muscles of the thigh, then rauschbrand bacilli were found also at the latter point. A sterilized infusion of muscles thus affected, injected into another rabbit, produced somnolence. If, at the same time, the injected animal were also inoculated with virulent rauschbrand it quickly died; but if the inoculation were postponed twenty-four hours it became in the mean time insusceptible.

FARCY: GLANDERS.

Various authors have described from a clinical point of view four varieties of this infectious malady, which have been described under the terms acute and chronic farcy and acute and chronic glanders; under the former term grouping those varieties in which the superficial tissues are the more affected, and under the latter those in which the deeper cavities, like the nasal fossæ, the lungs, and the deeper glands, are affected. To-day, however, these descriptions have much less importance, since we recognize the same infectious agent active in them all, and we know that by means of a lymphangitis extending from a farcy bud, we may be led to find a deep abscess, and that the deep ulcerations in the complicated cavities of the skull differ in no essential respect from those upon the skin.

Some of the difficulties of diagnosis in some of these cases may be gathered from such a case as the following which Bucquoy reported to the French Academy of Medicine in 1883: A young man, æt. 19, of alcoholic habits, and suffering from recent syphilis, was admitted into the hospital, displaying upon one leg a fungus ulcer as to whose origin he was entirely ignorant; and upon the thigh of the same side was a small fluctuating swelling of livid hue, quite like abscesses which one observes after contusions; his general condition seemed to be that of typhoid fever. On the fourteenth day after admission there appeared on each side of the ankle a phlegmonous swelling with redness and œdema; on account of this arthritis the diagnosis of typhoid was discarded and the case was regarded throughout as one of some septic or purulent infection. His condition became more serious; four days later he was delirious and other joints became involved after the same fashion, while the synovial cavities were distended with fluid; the abscess about the ankle was opened and considerable pus evacuated. On the following day he was unconscious, and a peculiar bullous eruption appeared all over the body. On account of this eruption the specific infection of glanders was suspected, although there were no nasal symptoms. He died twenty-two days after admission. The liver contained a large abscess and many of the joints contained pus. The true character of the disease was established by careful inquiry into his antecedents, which showed that he had come in contact with horses suffering with glanders, and by the results of inoculation of some of the fluids upon animals. An ass inoculated with some of this material developed a very typical swelling of the sub-maxillary glands, and died ten days after vaccination.

We do not at present recall any other case where the diagnosis was established or verified by such inoculation.

The specific organism of glanders, known as the *bacillus mallei*, has perhaps been the most carefully studied by Löffler. It is a little shorter and broader than the tubercle bacillus, varying but little in length. Commonly they are found in pairs side by side, often held together by a little hyaline material which takes no stain. In fluid media they show active molecular motion, but no spontaneous motility. The organism is peculiar in this respect, that by no means all of the bacilli form spores, and spore formation seems to occur only at times, upon the favorable surroundings. Reaction to staining media is peculiar, since these bacilli take no basic aniline dyes. They grow best on blood serum and potato, but may be cultivated in other media. They show about the same degree of resistance to heat and chemicals as other nonspore-bearing bacilli —are destroyed by exposure for ten minutes to a temperature of 55° C. The animals which are most susceptible are the horse, cow, sheep, guinea-pig, rabbit, white rat, cat, tiger and lion; while common pigs, dogs, the common rat and domestic fowl enjoy great immunity.

LECTURE VIII.

TUBERCULOSIS.

SYLLABUS. *Tuberculosis.*—Slowness of English and American writers to properly appreciate the matter of surgical tuberculosis. Tuberculosis of lymphatic glands; of bones; of joints; of tendon sheaths. Character of infectious granuloma everywhere the same.

SO much has been said and written about tuberculosis within the past ten years that it seems now hardly necessary to try to educate the professional public as it seemed a few years ago. It has always struck the writer as one of the curiosities of medicine that the English speaking people should be so slow to appreciate the frequency of tubercular processes in parts of the body aside from the lungs. Those who were thoroughly familiar with its pathology and clinical aspects in the lungs were yet extremely slow to acknowledge its common existence elsewhere. For instance, I recall one of my old and esteemed teachers, who, only fifteen years ago, took occasion to assure his classes that tubercle was never found in the bones. Such a statement as this was much worse than nothing, since it rendered many of his auditors in-disposed to pay that attention to the matter which it deserved; and so I have observed that, with a few striking exceptions, English and American authors alike have been extremely slow to recognize that which has long been recognized on the Continent. Such a thesis, for instance, as that of Nelaton, which was published over fifty years ago, and which contained illustrations fully equal to most of those which appear now, and in which he described carefully and explicitly both disseminated and confluent tubercle, has scarcely been alluded to by his English-speaking successors. These gentlemen, on the contrary, have gone on, some of them even to the present time, disregarding knowledge which could so easily be obtained, and describing scrofula of bones and glands as if no better information were at hand than was afforded one hundred years ago. A new school of young and accomplished pathologists has grown up in Great Britain and in this country, who have atoned in large measure for the wilful ignorance or misrepresentation of their elders—men, for instance, like Treves and Sutton, Senn and Gerster, and others, to whom the present generation is largely indebted for the insistence with which these views have been promulgated. Nevertheless so much literature is now at hand, even to the student who reads only his mother tongue, that it hardly seems necessary to attempt any general discussion of the disease in its surgical aspects, nor to do more than ask your attention to a few of its more interesting or less known phases. First of all with regard to its specific and infectious features, there is no time now in which to go over the experimental proof of the doctrine of specific infection. He who is not reasonably well informed in this topic will have little use for such lectures as these.

That the tubercle bacillus possesses facultative pyogenic powers has been shown in an earlier lecture. That most of the abscesses caused by breaking down of tubercular gummata, or of specific granulation tissue, are due to a secondary infection will be spoken of later. Our interest at present is rather in the direction of certain manifestations of the disease with reference to tracing, if possible, the port of entry of the specific germs, or the path of infection. It may be said, however, with regard to the cold abscesses which so often result from slow tubercular processes, that bacilli are relatively seldom found in their puruloid. This failure to find them is easily explained, since in many of these cases the puruloid collection is months or even years old, and all living organisms have long since died out in such material. On the contrary, the original membrane or condensed layer of cells, by which protection was at first afforded the healthy tissues against infection, has become more and more firmly organized and still constitutes the membrane to which the old and entirely improper term pyogenic was misapplied. It was shown early in this course of lectures that the proper distinction for this membrane should be *pyophylactic*, implying the protection which it really affords. In certain other cases of recent cold abscesses, the microscope and the culture medium yield no evidence of bacilli, while, nevertheless, inoculation experiments succeed. This is to be explained through the medium of spores which are unrecognizable by other methods, but which manifest their specific peculiarities when planted in the living animal.

Tuberculosis of lymphatic nodes.—These comprise practically all the glandular manifestations which the old writers grouped under the head of struma or scrofula. When these cases belong to the category of the surgical, they are usually cases where the point of inoculation is more or less removed from the gland or glands involved. Any lesion of cutaneous or mucous surface, recent or old, may lead to this. In the mouth, for instance, a mucous patch, a canker sore, a diseased tooth, an inflamed tonsil, may serve equally well. Whereas on the body surface any abrasion or pathological defect may afford a port of entry, although the germ may be transmitted to the nearest lymph gland, and the lesion through which it enters may heal without any visible reminder of the previous infection.

The lymphatic nodes in the neck, for instance, may be affected as the result of some skin disease of the face or head, of which eczema is the most common form, or through diseased eyelids, as the result of catarrhal or specific ulcers in the nose; of a diseased middle ear, or through any dental or mucous lesion in the mouth or pharynx. The nodes act as filters and become blocked or plugged as do many other filters, by which obstruction a limitation of infection is for an indefinite time produced. This is brought about in effect by an inflammation, *i. e.*, a lymphadenitis by whose inflammatory products the lymph channels are obstructed. Along with this goes usually a certain degree of peri-adenitis, by which perhaps still further protection is afforded. The tubercle bacillus is non-motile, and infection of nodes which are not in the direct course of the lymph stream must probably be explained by conveyance through the agency of migrating amoeboid cells. It is of interest, also, to remember that infection is spread usually through glands belonging to a definite regional system. Thus if it be one of the deep glands which is first infected, it is those belonging to the deeper group which become later involved. Nevertheless as there are connecting branches between the two systems infection may spread from one to the other. As long as infection is confined to the nodes the patient is protected against miliary invasion. So soon, however, as the last lymphatic glandular filter has been passed, dissemination must and will readily follow.

Tuberculosis of bone.—Next to the nodes the bones are most frequently involved, and most so in children. The favorite location is in the neighborhood of the epiphysis of long bones; next, most commonly in the cancellous tissue of the short and irregular bones. We can scarcely imagine a primary tuberculosis of an unexposed bone, consequently, disease of this kind is always a sign of a previous and, perhaps, concealed lesion. When bacilli are once floated loose in the blood-stream they are more likely to be entangled by this peculiar tissue, growing bone, than by any other part of the body. We have, as it were, a mycotic embolism of a minute artery, the fixation of which gives ready impetus to the formation of a minute nodule of infectious granuloma. It is well known that the typical manifestations of tuberculosis in a bone consist of a conical infarct or sequestrum, and König taught that this was due to an occlusion of a small artery by a tubercular embolus; while Mueller, one of his pupils, proved the accuracy of this view by direct intra-vascular injection.

It is to one point, especially, in connection with bone tuberculosis that I desire to allude at this time, and that is to a form of acute miliary tubercular osteomyelitis corresponding in bone to acute miliary tuberculosis in the lung. Its clinical manifestations are not so very different from those of the acute infectious variety due to pyogenic infection, save that they are a little less acute. There are not the fulminating attacks, nor the intense pain which characterizes the latter form, and, yet, it may be followed by nearly as much local destruction. Nor is it likely to be so early recognized, nor does it perhaps call for quite as early radical treatment. Moreover, if allowed to go for a time unrecognized it is not so likely to determine the death of the individual, since spontaneous relief, after a fashion, is more commonly afforded. This form of disease is described alike by French and German writers; but I have never seen any reference to it in English. König makes it the fourth of his forms of osteo-tuberculosis, and Kiener and Charvot gave it a somewhat imperfect description a few years ago. The periosteum is more commonly involved than in other forms, and there is no tendency to regularity or limitation in the formation of sequestra. It has been my lot to meet with several cases of this kind for which more than once I have had to practice amputation. The last distinctive case which I saw was one of nearly total necrosis of the shaft of the tibia, with spontaneous perforation of the skin in the endeavor to eliminate the sequestrum, which consisted of this diaphysis. This had been regarded at first as a case of acute rheumatism.

I think we have also a sub-form of this character where the acuteness of the disease consists simply in an exacerbation of an old and latent focus in the same bone.

This condition may be fatal, sometimes by intensity of a mixed infection from the introduction of a septic element, or sometimes by metastatic and general miliary disease.

Tuberculosis of joints.—A large proportion, especially in children, of tubercular joints, are really in effect extensions of tubercular foci in adjoining bones. Nevertheless, a form of primary synovial tuberculosis is known, and is more frequent the adult. Tubercular infection of a previously healthy joint presupposes the entrance of the germ through the respiratory tract, alimentary canal, or some surface lesion. The growth of co-called fungus granulation tissue into a joint is precisely similar to its growth or formation in a tendon sheath, and may be thus described. It is well known that wherever tubercle bacilli lodge, they act as specific irritants, which produce granulation tissue of a well-known type. This granulation tissue, as it forms, has the power of making way for itself in any and every direction, and the firmest and thickest bone will melt away before its advancing pressure, as it does before that of an aneurism. This tissue may gradually replace the cancellous tissue of the head of a bone, and finally escape by one or more perforations of this compact shell to burrow underneath the periosteum and work its way toward the skin, or to perforate articular cartilages and proliferate within a joint cavity. Wherever it appears it is always the same in structure, although sometimes more compact, or at other times more œdematous. It often happens that the free space of a synovial cavity is filled up with this tissue, which becomes more or less condensed, and which disintegrates, and in many ways affects the surrounding, previously healthy tissues, before a drop of pus is formed. It is seldom under these circumstances that the tubercle bacilli evince any pyogenic properties by themselves; but a mixed infection is likely to occur at any time and secondary pyogenic infection does in fact occur sooner or later in every case. The result of this is that this granulomatous tissue of low vitality breaks down very easily, and we have, as the consequence, an abscess formation and all the well-known phenomena of the later stages of white swellings. Of course, if at any point this granulation tissue has perforated the skin, local infection necessarily occurs, otherwise the infection is usually through internal channels.

This same condition of affairs obtains when we have to do with tuberculosis of tendon sheaths. Hueter called this affection *tendo vaginitis granulosa*, and the granulation or fungus tissue with which these sheaths are often filled has precisely the same origin and significance as above. Furthermore, Riedel has shown us that the rice-grain bodies so often found in hygromata of tendon sheaths always indicate synovial tuberculosis. This condition is most common as the extension of a tubercular process along tendon sheaths, following perforation of a tubercular joint, but is now known to be also a primary lesion. When primary it is usually an embolic infection, which when once begun pursues everywhere a typical course. The tendon itself is usually covered with a thin layer of the same granulation tissue, and may be so weakened as to easily rupture.

When the disease is primary in a tendon sheath, an adjoining joint may easily become secondarily affected. When the fungous granulations forming hard white masses are separated by friction, the so-called rice-grained bodies are formed, or else they are the product of a peculiar fibrinous inflammation and exudate. The disease is most common in the wrist, next most so about the ankle.

Dmochowski has investigated the tonsils in fifteen consump tive patients, and in each case discovered more or less outspoken evidence of local tuberculosis. The naked eye appearances were scarcely altered, but the epithelial cells of the crypts die soon after infection, and, finally, produce a superficial dead layer. After this we may have the tonsils studded with miliary nodules, or these may coalesce and the whole gland become little less than a tubercular gumma.

A similar infection of the mammary gland I have elsewhere described. (See *American System of Gynæcology*, Vol. 2, p. 358). The commonest manifestation of mammary tuberculosis is to be met with in the form of cold abscess and chronic fistula; aside from these we have to deal with disseminated tubercle, and tuberculous gumma; local infection having occurred the disease takes much the same course as in the lungs. Multiple true tubercles are formed, which may for some time remain separate, or they coalesce, in which case we have the confluent form. To these succeed caseation, which may be followed by atrophy and more or less calcification, or there develop cold abscesses as the result of a degenerative process, or acute abscess as the result of mixed infection. Probably a true miliary form exists, but has not yet been generally recognized, perhaps, because patients presenting it are not seen sufficiently early, *i. e.*, have passed this stage by the time they apply for treatment.

And so it goes on all over the body, there is no part which is exempt from liability to tubercular infection, and tubercular processes are everywhere essentially the same, modified only by character of tissue and nature of environment. Every surgeon of experience sees astonishing manifestations of the penetrating and permeating power of this peculiar granulation tissue; the toughest and strongest fasciæ are perforated by it as is the copper sheathing of large vessels perforated by various salt water parasites, while at the same time masses of this tissue are deflected, as it were, or turned aside and made to take most unexpected directions by the resistance which a thin layer of fascia will interpose. An intelligent comprehension of infectious granulomatous tissue, and its properties, will enable a ready understanding of such processes as caries, necrosis and spontaneous separation of sequestra, as well as of the clinical features of white swellings and ganglia and a variety of other common manifestations of tubercule, which I regret to say are so often the bug-bear of students, and of all those who are not grounded in pathology.

Probably the most difficult of the many problems which a study of this disease offers is that concerning the source of the infectious element and its hibernation for an indefinite time in some concealed part of the system. Evidence has of late accumulated to show that in the deep collection of lymph nodes we often have both concealed and long standing foci of infection which, like powder mines, give rise to sudden explosions.

In 1887 Bollinger carefully examined the bronchial lymph-nodes of a large number of children who died during a severe epidemic of the measles. He demonstrated that tuberculosis may be latent in a child apparently in perfect health, and he found abundant bacilli in the lymphatic nodes at the roots of the lungs, and in the mediastinum, in children who were free from tubercule in the lungs proper or other parts of the body. Also it has been demonstrated by numerous observers that children may have for a long time latent glandular tuberculosis before phthisis develops, since in children the lymphatic nodes are in a high state of functional activity.

Loomis (*Med. Record.*, Dec. 20, 1890,) and Northrup (*N. Y. Med. Jour.*, Feb. 21, 1891,) have lately made important communications showing how the primary infection of tubercle, especially in children, often occurs in the bronchial lymph nodes. Loomis reports, for instance, such an autopsy as follows: A young woman æt. 26, who enjoyed perfect health to within four weeks of her death, was seized with fever and chills, which led first to a diagnosis of malarial fever that was afterwards changed to that of general pulmonary tuberculosis. At the autopsy the lungs were found studded with fresh tubercles. No old tuberculosis was found in the lungs, nor could any point of infection be found *except one large bronchial gland* which presented all the characteristic changes of an old tubercular process. He mentions also a case presented to the New York Pathological Society by Dr. Van Giesen, of an infected bronchial gland, evidently tubercular, removed from a person dying from phosphorus poisoning. No tubercles were found in any other part of the body. These gentlemen have made it so very clear, by their own cases and those which they have collected, that the internal glands may be long and latently subject to tuberculosis before they disseminate the disease, that I think we have large reason to take the ground that infection of parts which interest the surgeon may occur with equal ease from these internal sources. Considering that the life-stream is from the lungs toward the lymphatic nodes, it is not more difficult to imagine how a lung may be affected from this source than how a bone at some distance may be. They are probably conveyed into the veins first, after which they are easily distributed to distant parts of the body.

Müller, commenting upon 500 autopsies in children with respect to the frequency of tuberculosis, regards the lungs and next to them the bronchial glands as the most common paths of infection by tubercular processes. He recognizes the fact that the glandular infection may be primary, in which case the lungs are secondarily involved by contiguity, in which case also the apices are not the parts first involved. It is characteristic of tuberculosis in children that the lymph glands should be early involved; 170 times out of 209 cases was this the case, and of these 170 the bronchial glands were involved in 131.

Next to these stood the mesenteric, 78 times; the cervical, 17; the mediastinal, 16; retro-peritoneal, 10; portal, 7; epigastric, 6; inguinal and retro-maxillary, each 3. Tuberculosis of the bones and joints occurs most often in the fourth year of life.

Sprengel has called attention to the importance of a previous tubercular infection of the skin or mucous membrane by which open disease may be produced, either through the lymph stream or the arterial. It is necessary also not to overlook the existence of primary infection through inherited, *i. e.*, congenital tuberculosis. All writers on the subject agree that the tubercular process often remains latent for a long time, by latent meaning localized, and that generalization is especially favored by any disease which causes prostration, as also by certain specific diseases, like measles, scarlatina, pneumonia, diphtheria, puerperal fever, etc. This generalization is effected sometimes by the lymph system, much more often through the blood system; thus out of five hundred cases of tubercular disease, eighty-six were of the general miliary form, nineteen of these of the most acute type. Müller finally lays considerable stress upon a peculiar form of tubercular disease in children, characterized by a tendency to caseation, as an instance of which we have the relative frequency of caseous pneumonias.

Demme has recently reported some interesting observations in this same field, one of them being that of an infant of six months, that displayed a tubercular ulceration over the left breast. He considered it most probable in this instance that he had to deal with a tubercular infection involving a small abscess which had resulted from a limited mastitis directly after birth, since the mother and sisters of the child, who were themselves suffering from consumption, often applied to the ulcerated surface one of their soiled handkerchiefs. Another case was that of multiple tubercular disease of the mouth in an 8-year-old, predisposed, girl, who suffered at the time from pulmonary lesions, and who died of acute generalized miliary disease. The affection presented a remarkable similarity to mucous patches, and had been mistaken for inherited syphilis. Antiseptic treatment produced no effect, however, and tubercle bacilli were found in the local lesions.

A third case was that of a tubercular meningitis following quickly after injury to the skull, in a child previously healthy. At the autopsy the pia was found studded with miliary tubercles, and an old tubercular bronchial gland was recognized. In such case as this it is probable that almost any injury may prove sufficient to determine an outbreak of tuberculosis.

Tricomi has reported a case of joint tuberculosis which manifested itself in the early years of childhood, and apparently healed with anchylosis of the joint. Seventeen years later after forcible efforts had been made to straighten the limb the patient died of general tuberculosis. Examination of the joint revealed old tuberculous foci which had communicated with the joint, with the typical features of fungous arthritis. The internal organs were studied with miliary tubercles, all fresh, showing nowhere any old lesion save in the joint. He interprets the case with propriety as in all probability demonstrating the possib'e long period of latency and the fresh eruption after operative provocation. (*Giornale internaz. delle scienze mediche.*, 1886, 8, p. 628.)

LECTURE VIII. (CONTINUED).

CONCERNING MIXED AND SECONDARY INFECTIONS.

SYLLABUS.—*Introduction to the study of mixed and secondary infection:* Definition of the terms. Their evidences met with everywhere about the body. The most interesting effects, for the surgeon, are met with in the bones and joints. *Dysentery. Cholera. Hydatid cysts.*

MIXED INFECTION is a term applied to those collections of pathogenic organisms in which we find more than one variety of microbe. Thus in a recent tubercular abscess we may find both tubercle bacilli and pyogenic cocci; in a post-typhoid abscess both the latter and the distinctive bacillus of typhoid, or in a post scarlatinal suppuration beside the true pyogenic agents there may be found one or more bacterial forms supposed to be in some way related to the fever. In the pus of a gonorrhœal bubo, for instance, I have found beside the ordinary pus organisms the specific coccus of Neisser. Mixed infection is usually easy enough to demonstrate; it is much more difficult to make out the order of attack, though *a priori* we can usually indicate it. Post-febrile collections of pus constitute our most common and most illustrative instances. For example I have myself recognized pyogenic cocci (mostly streptococci) in post-scarlatinal intra-articular abscess, along with one or two other forms whose exact determination I could not make out. A case much like this was reported in 1884 by Heubner and Bahrdt in which retro-pharyngeal abscess and purulent synovitis were met with. There appears to be but one explanation of these cases: As the result of the impregnation of the blood and lymph by poisons resulting from the febrile disease the resistance of the tissues is diminished, and cells now succumb to bacterial invasion which before would have successfully withstood it. If one will consider the large area exposed to contact with the source of poison in cases of, say, gastro-intestinal catarrh, typhoid fever, or in the infected uterus *post-partum*, he will see how favorable is every condition for permitting such a toxæmia to take place by absorption. The peculiar effects thus due to toxæmia are discussed in another place.

The occurrence of joint inflammations of various degrees of severity in the course of or following the various infectious diseases, has long been recognized, although their exact relationships have only been made out within the present century. Whether such inflammations were mere accidents or coincidences, or whether they bore the relationship of cause and effect, has only been cleared up since the science of bacteriology has shed light upon this very abstruse topic. For instance, the synovial effusions accompanying acute inflammatory rheumatism are among its most prominent clinical features. If now in unusual cases this effusion shall take on the purulent character so that we have to deal with an acute abscess in the cavity of the joint, it is a matter of no small importance to determine whether rheumatism by itself can ever produce abscess, or whether an entirely different and more or less independent condition has been produced. Until bacteriologists had completely established the fact that there is no suppuration without bacteria, this point could not be cleared up. As the matter stands to-day, the parasitic nature of acute rheumatism not being established, we are compelled to conclude that upon the primary condition of serous exudate there has been grafted a second and more serious condition of microbial infection of material which has already left the blood vessels. This is a fair sample of what should be spoken of as primary infection. The term *Secondary Infection* is intended to convey a somewhat different meaning. Under this name are comprised those conditions where, upon that caused primarily by bacteria of one species, there is engrafted another infection due to microbes of a different species. To illustrate this statement a little, take a gumma of tubercular or syphilitic origin in which there are no evidences of suppuration. This may exist for weeks or months in form almost unaltered. From some cause or other, be it easy or difficult of explanation, an infection of this specific granulation tissue by pyogenic bacteria takes place, and then we have the rapid formation of an abscess. Again in the lungs more or less infiltrated with tubercular tissue, the same kind of pyogenic infection takes place; and cavities or excavations are rapidly formed. (This without reference to the fact that tubercle bacilli may of themselves develop pyogenic powers). Yet another illustration: In the well-known form of gonorrhœal arthritis met with most often in the knee, numerous investigators have found gonococci in the effused fluid. It has already been shown (see Lectures III and X) that gonococci by themselves are not pyogenic. So long as no secondary infection by the ordinary pyogenic bacteria occurs, this fluid remains serous or serofibrinous; but if such secondary infection do occur, there is rapid formation of a genuine pyarthrosis. These illustrations serve better to define what is meant by mixed infection than would statements alone without illustration. By quite similar process we have the conversion of a tubercular pleurisy or pleuro-pneumonia with effusion into an empyæma; of an originally tubercular meningitis into the suppurative form, and of many other well known conditions.

De Wildt (Diss. Utrecht, October, 1889) demonstrated that the exudate from a case of serous inflammation makes an excellent culture material for pyogenic organisms by tying a broad band tightly around the base of a rabbit's ear, and then applying very hot water for a few moments to the ligated part.

The consequent serous exudate was, by the injection of small quantities of staphylococci, so affected that very quickly a profuse suppuration occurred. Control experiments without the previous irritation of the ear, gave no result. This is of interest as showing how the exudates in rheumatism are easily infected. It is furthermore known that fungous joint inflammation, in other words tubercular infection, occurs occasionally after acute rheumatic affection of the joints. This fungus condition is of course nothing but a primary tubercular infection occurring in the same way as suppuration. Upon this fungous condition may occur a second infection of pyogenic cocci, so that we have three entirely different lesions of the same joint. First, acute rheumatic synovitis; second, tubercular infection of the joint; and third, and much later, suppuration and degeneration. Not a few of these secondarily infected cases occur as results of extension of infection and embolic pyæmia. It is not difficult to account for the secondary infection in such cases. It can occur, for instance, through diphtheritic infection of the pharynx, or follicular abscess in the tonsils; perhaps more commonly from the pharynx than from any other locality. Indeed so common is such infection from unsuspected or concealed sources that Greisinger described what he called a suppurative diathesis, which had in itself much of what we speak of as hospitalism. That the system is left in a more than ordinarily vulnerable condition, with lowered susceptibility or power of vital resistance, after various acute infectious diseases, is well known. The ease with which many such individuals succumb to tuberculous processes, or the manifestation of acute so-called scrofulous lesions is only too frequent. Perhaps more than any other disease, measles leads to this condition, and Luecke, among others, has called special attention to the frequency of joint and bone diseases following soon after this disease.

I think it proper to make a distinction between *secondary* and *mixed* infection, limiting the former term to those cases where a fairly distinct sequence of events can be observed, and applying the latter term to those where complex or multiple infections occur at or about the same time. This latter I consider to be the case in many instances, as in the contraction, often, of diphtheria, gonorrhœa, puerperal fever, dissecting wounds, etc. And in other lectures in this series I have called attention to the added morbific effect of introducing two widely variant species at the same time. There is much to show, therefore, that a mixed infection is oftentimes worse than a simple form.

It is worth while to remember, in this connection, the peculiarity of the *kefir* ferment. This is complex, and is composed of three different organisms, each of which can be cultivated alone; but the peculiar fermentative action essential to the production of *kefir* is only brought about by the combined activity of all three forms.

From what has been already said, it will be more readily apprehended how some previously inexplicable conditions have been brought about. For instance, the formation of a hydrops articuli, and then the subsequent spontaneous dislocation of the joint; and an important therapeutic rule may be from such cases deduced, viz., that when a joint is so involved it needs to be handled with extreme caution, and carefully watched for a long time. Massage, which is ordinarily of so much efficiency in the dispersion of joint effusions, would be in such a case most undesirable, since by dispersion of the fluid might be precipitated a metastatic infection of various other parts of the body. So, too, with aspiration or incision for removal of the fluid. No matter how carefully performed, it would be theoretically impossible to avoid infection of tissues between skin and synovial membrane, and the path for a general infection might thus be made. If, indeed, such operative measures must be resorted to it would be desirable to follow them with intra-articular injection of emulsions containing iodoform. By such a measure not only is protection instituted, but an antidote to local infection is at the same time introduced.

The various inflammations of bone following acute infectious disease are not so often met with nor so well known as those of the joints. Nevertheless they occasionally occur, and when acute, are usually of such extreme severity that the crisis occurs within a few days at most.

Maisonneuve and Chassaignac were among the first to point out that there is a form of periostitis following typhoid, scarlatina, small-pox, etc., of frequently increasing severity, and it is mainly to the French writers that we owe our knowledge of this condition. Later Luecke showed how not merely periostitis but even more acute forms of osteomyelitis resulted from the infectious diseases. This was in 1880, while a year or two before this Langenbeck had warned the Congress of German Surgeons that surgeons generally had hitherto laid altogether too little weight upon the relationships between inflammations of bone and other acute diseases, and had paid a disproportionate amount of attention to traumatic and rheumatic causes. These observations of Langenbeck's were discussed by Ponfick in a lecture upon necrosis of bone marrow following relapsing fever. The same surgeon published in 1872 and 1873, in Virchow *Archives*, further contributions to the behavior of bone marrow in cases of typhoid fever. A little later Freund continued the studies of his teacher Ponfick, and shed much more light upon the subject. Among others Ebermaier, examining the ribs of a patient dying during the fourth week of typhoid fever, found typhoid bacilli in their marrow, and showed, as did Freund also, how favorably conditioned the marrow is for the development of such organisms. Fischer showed that in all the infectious diseases the periosteum of the entire skeleton becomes more vascular and succulent, and is detached with much greater ease than in the normal condition. In other words, the lower layer of cells of the periosteum, as well as that cellular layer which surrounds the vessels entering the bone, is attacked in the same way as the soft parts at a greater distance from the bone, and this condition is summed up in the expression that inflammation of the bone is virtually inflammation of the soft parts around it. It is not unfair to view the involvement of the bone marrow and the tissues outside of it in the same way as we view the alterations in the spleen; they are of nearly the same general character.

Neve, in an article elsewhere alluded to, speaking of a fact that organs of such size and function as bones and joints frequently suffer after septic fevers, alludes to the intimate nervous and vascular relationship of the joints with their over-lying skin, the similarity of epithelium, the rôle of the medulla in the formation of the blood and the vascularity of the sheathing of the bone; and in the case of the teeth and alveolar process their dermal origin and exceedingly active and developmental changes, by which participation in the morbid process set up by septic poisons is favored.

Authors have described a peculiar form of necrosis of the alveolar process, with more or less destruction of the jaw bone, peculiar to the eruptive fevers and much resembling that from fumes of phosphorus. In this case it would seem as if the essential nature of the lesion was a poisoning, in one case (phosphorus) from without, *i. e.*, from an extraneous source, in the other from within. Mr. Salter has called attention to a peculiar coincidence in this matter, since, in the jaw necrosis of eruptive fevers, the poison is generated in the organism and affects the teeth and teeth pulps by reason of their being dermal organs; in other words members of the tegumentary system, upon which system generally the poisons spend their chief destructive force. These cases occur commonly in children, and usually in those of low state of vitality, evident both in their general systems and their teeth. Salter has also called attention to the extremely slight changes in nutrition which occur in teeth when once they are formed, by which consequently they are removed to a large extent from possibility of repair from acute disturbances.

From the time of birth to the eighth or ninth year the jaw bones are the seat of intense development in the formation of teeth,and are among the most vascular parts of the body. About the middle of the period named, that is about the fifth year of age, the jaws contain no less than forty-eight developing teeth and tooth-germs. It is at about this time that the poisoning of the exanthematous fevers appears to exert its most marked effects upon the dental system. Salter appears to have been among the first to recognize necrosis of the alveolar edge and shedding of the teeth as one of the sequelæ of these fevers. This particular gangrenous tendency seems to be almost peculiar to the eruptive fevers, including typhoid under this heading, though even here it is very rare. In order of frequency it is most commonly met with after scarlet fever; measles and small-pox coming along second and third. Whether the gangrenous process alluded to in the above remarks is of the nature of a specific one, in other words whether it is the result of a mixed or secondary infection, or whether it be due to circulatory disturbances, is not known; nor do I know of any bacteriological researches concerning the matter.

When in the course of a purulent infection one sees the development of a suppurative arthritis, it is logical and necessary to admit the relation of cause and effect between the febrile condition and the manifestation in the joint. With this statement Lapersonne begins his monograph on *Non-Tubercular Infectious Arthritis*, a work, in the writer's estimation, of very great value. Nearly a century ago Bonnet gave up a chapter in his great work on Diseases of the Joints, to what he called consecutive rheumatisms, which he carefully warned us were not to be confounded with genuine rheumatisms. Since his time we have studied with great care blennorrhagic purulent arthritis of septic or puerperal origin, and the various arthritides which follow infectious fevers, and have arrived now at a very different period, when these matters have to be studied mainly in their bacteriological aspects. Lannelongue has made out five varieties of arthritis as follows:

1. Traumatic arthritis.
2. Inflammatory arthritis, caused by extension from surrounding inflammations.
3. Generalized arthritis due to rheumatism or gout.
4. Arthritis due to nervous or cord disease, such as progressive muscular ataxy.
5. Septic arthritis, parasitic or virulent, virtually of microbic origin, and secondary to some general disease.

This last may be regarded virtually as infectious arthritis, and is the only form which concerns us here. A few years ago Bouchard made the following statement: "Parasitism is established with certainty for four diseases of men, anthrax, glanders, tuberculosis, and malignant œdema, while it is almost established for gonorrhœa and erysipelas." It is simply an evidence of what rapid progresss we are making that within so few years, namely, about six or seven, this list has to be so greatly extended. It is necessary now only to show that a given disease is of parasitic origin, in other words infectious, to convince one that various complications may be met with during its course or after convalescence; and it is quite likely that the near future will add several names to the list as it stands to-day. For the surgeon the joint complications of these various diseases have a peculiar and wide importance, not merely because of the serious nature of many of these manifestations, nor because of their relative frequency, although abscess in the joint will be met with probably fifty times to one abscess in the liver or any of the viscera.

Another reason why these lesions stand out so prominently in our interest at present, is because since the *renaissance* of surgery which bacteriological study has brought about, we have at last the explanation of that for which, in time past, many, and sometimes absurd theories were invoked. I do not mean that everything is yet clear, but I am certainly of the opinion that matters have been greatly cleared up for us since Koch and Pasteur began their work.

One of the greatest difficulties in the study of these lesions is that of accurate classification. Is one to speak of them according to the number of joints involved, according to the disease in the course of which the lesion appears, or according to the organism which appears to be particularly at fault? In other words, shall one speak of a mon-articular or bin-articular, or of a post-typhoidal, or of a bacillar abscess, or how? It seems to me that the best nomenclature is that which I have tried to use throughout this essay, and to speak, for instance, of a mon-articular post-gonorrhœal synovitis, or a post-puerperal poly-articular purulent arthritis; endeavoring to convey in the fewest possible words the largest amount of information.

As a matter of fact not until the fluid or pus from these cases has been examined can we say whether common pathogenic forms or specific disease germs are the active agents. To name them, then, after this plan would be to wait some days or weeks until after a post-operative or post-mortem diagnosis could be made. Teissier and his scholars, like Griesinger, have introduced the term purulent diathesis, and by the use of it have explained certain cases of spontaneous septicæmia and pyæmia. The very term indicates the necessity of more accurate knowledge, and must be relegated to the past, although if it could be confined to a description, in an adjective sense, of lowered or increased susceptibility to certain organizations by which apparently suppuration is encouraged, providing the necessary germ to be present, it might be applicable. In 1871 Quinquand described under the name *maladie arthrito-phlegmoneuse*, an infection characterized by multiple suppurations about the joints and in the cellur tissue, and formulated the following conclusions: "There exists a disease of special nature, characterized by articular and phlegmonous lesions, which have a strong resemblance to each other, and this I propose to describe under the above name. It comprises three forms, *a*, the arthrito-phlegmonous form in which there are moderate fever, acute suppurative arthritis with rapid destruction of cartilages and epiphyses, and subcutaneous indurations which later suppurate; *b*, an articular form characterized by destructive changes limited to the joint; and *c*, a phlegmonous form in which the lesions are extra-articular, and occur in the cellular tissue. This disease is distinct from rheumatism, although it somewhat resembles it, and develops under the influence of fatigue, of certain traumatisms or burns, and sometimes from causes quite unknown." He publishes as an illustration of this disease the case of a robust man of healthy antecedents, who burned his arm one day and received an excessive fright. Soon after he had a violent chill, vomited, and became seriously ill, and developed the articular manifestations of the condition just described. Abscesses developed at various points, he rapidly grew worse, a bed-sore formed over the sacrum, delirium supervened, and the disease proved rapidly fatal. At the autopsy extensive destruction of the soft and hard tissues was found. From the standpoint of to-day it would scarcely seem necessary to erect a separate form of disease to accommodate such cases as these. Ample opportunity for infection was offered from the burned surface, while, undoubtedly, the emotional and nervous elements conspired to materially reduce his vitality. So in such a case as that brought forward by Tuffier, as one of sporadic or spontaneous pyæmia, in which a trifling uterine affection had been treated by very superficial applications of the actual cautery, which were followed by very rapid fatal purulent infection. Even so, with such a case as one with which I was myself conversant, where the only explanation for a fatal case of pyæmia was afforded by the discovery of a minute but fatal bursal suppuration under a small soft corn. Surely for such cases as these it is no longer necessary to suppose a purulent diathesis, any more than it is for a case of septicæmia following a dissection wound.

Among the first to regard these mixed and secondary infections from the clinical side was Dr. Keen ("On the Surgical Complications and Sequels of the Continued Fevers." Four Lectures, No. V. Smithsonian Collections). A lively interest in the subject awakened by his paper prompted me to report a number of cases from my own experience, in 1885 ("Some of the Surgical Sequelæ of the Exanthems and Continued Fevers," *Canadian Practitioner*, July, 1885), working still from the clinical standpoint. Since the introduction of bacteriological methods these problems have now to be studied in a very different and even more interesting light. The two monographs which most fully cover the ground, in my estimation, are those of de Lapersonne, "Des Arthrites Infectieuses," Paris, 1886, and Witzel, "Die Gelenk und Knochenentzundungen bei Acut-Infectiosen Erkrankungen," Bonn, 1890, to which I desire to acknowledge large obligations, and to which I must refer for a bibliography of the subject.

I propose to devote the remainder of this course of lectures to a consideration of these secondary and mixed infections, following the more important or common infectious diseases which have most interest for the surgeon, hoping at least to be instructive and suggestive in the effort, but not claiming that it is in any sense exhaustive of the subject.

DYSENTERY.

Dysentery is one of the special diseases whose joint complications have been recognized from the oldest times. Mild forms of this trouble have been noted in a great many cases as a common sequel; but such disturbances as suppuration in the joints are quite rare.

In Hippocrates we find the following remark:

"*Intempestive suppressa intestinorum difficultas abscessum in costis aut visceribus aut articulis inducit.*" At least three authors in past centuries have noticed actual joint suppurations in epidemics of dysentery. These are Strack, Zimmermann and De la Cloture. Experiences of the extensive epidemic which raged in Minz in 1757, and for two years later, laid the ground-work for the treatise on dysentery in which Strack expressed himself thus: "If the dysenteric poison affects only the chest it causes asthma; if the limbs, it produces arthritis; if both, abscesses." Zimmermann saw in those remedies used to suddenly check the discharges the causes of those joint pains and swellings which so frequently occurred in an epidemic during 1765 in Canton Bern. During the same year De la Cloture observed an epidemic in Caèn in which, so soon as the intestinal symptoms subsided, there were frequently suppurations in the joints which often led to anchylosis, and sometimes to death. The same author alludes also to a very fatal epidemic of the same character two years later in Forges, as a result of which a large proportion of the surviving patients remained lame, or suffered very serious pains in the extremities. He regarded these lesions in the limbs either as a metastasis, by which intestinal affection was terminated, or else as a chronic expression of the dysenteric disease. The years in the middle of this eighteenth century appear to have been marked by dysenterous epidemics of the same general nature in various parts of Europe. During one in 1776 and 1777 in Berlin, Stoll frequently observed the intimate connection of joint inflammations and dysentery; with the sudden subsidence of the latter there were frequently joint neuralgias or swellings or other inflammatory phenomena. These were very frequently spoken of at the time as rheumatic pains and swellings, which denomination appears to have been unfortunate, since there was nothing then, nor is there now, to indicate a genuine rheumatic character for these troubles. Moreover, Stoll relates that he occasionally found pus in the joints. The generally painful nature of these complications will account for the statement found in many treatises that rheumatism of the joints is an occasional sequel of dysentery. Indeed

Trousseau instituted a rheumatic form of arthritis following it. According to Trousseau, the joint symptoms were usually limited to the knee, and sometimes attained such a degree as to lead to the destruction of the capsule. A more nearly rheumatic character is given to these sequelæ by the fact that they sometimes do assume a wandering character.

Post-dysenteric arthritis has in very recent times been noted by Lecard in an epidemic at Rochelle in 1873–1874, who reported eight cases; by Aron and Joigny in 1876, who saw four cases; by Fradet, who in 1884 reported eighteen cases during an epidemic at Vincennes. Bérenger–Féraud in his treatise on dysentery speaks of diverse neuralgias and reports a case of arthritis along with conjunctivitis and cardiac complication. On the other hand observers of large experience have gone through other epidemics without seeing any such cases.

Thomas, of Tours, has furnished a rare instance of suppurative arthritis consecutive to dysentery. It occured in a lad of twelve, the violence of whose dysentery was followed by an eruption which resembled variola, on the second day articular manifestations appeared in various joints. By the fortieth day suppuration in these joints was positive. He yielded to the violence of the disease, and on autopsy nearly all the joints showed suppurative and some of them destructive lesions.

Post-dysenteric arthritis has given rise to much discussion and several theories. Thus Zimmerman was inclined to attribute it to the bad effect of drugs administered during the disease. It is still a question with certain writers whether there is a special form of dysentery, or whether there is any real identity between rheumatism and dysentery, or whether a rheumatic diathesis can be intensified by intestinal inflammation. Trousseau, for instance, admitted a rheumatic form of dysentery, while some others, like Stoll, or even so far back as Coelius and Aurelianus, believed in the identity of dysentery and rheumatism, while among the advocates of the third or latter view appears Thomas of Tours. Trousseau in speaking of the abdominal distress says that pain and tenesmus are more extreme in these cases than in those of any other form, and on the other hand it may be admitted that the great majority of these individuals present neither history of previous rheumatic attacks nor of rheumatic antecedents.

Two French writers have shed considerable light upon this subject. Huette based his work on dysenteric arthritis not only on historical considerations, but upon a description of ten personal cases. Quinquand, writing upon rheumatoid manifestations of dysentery, refers especially to the ætiological aspects of the subject. Kraeuter, referring to a complicated case of this character, held that the joint lesion, as well as the conjunctivitis, sometimes noted, depended upon a putrefaction produced by immediate resorption of fæcal material into the blood. This, written in 1871, is but a more modern expression of views held a century before by Zimmermann and Stoll.

Rheumatoid affections of the joints usually occur in the period of convalescence after dysentery in either the epidemic or the sporadic form. They occur sometimes a few days, sometimes a few weeks later, and present themselves ordinarily in much the form of a common chronic rheumatism. Sometimes, however, the attacks are quite acute. According to Raymund exposure and violence or over use are the most common causes. Mildness of disease of the dysenteric form does not necessarily secure immunity from these later complications. Almost all writers on the subject agree that it is the more acute or rapidly running attacks of the former, which produce the later.

For instance, Huette reports the following case: The sickness of the mother was mild and lasted fourteen days; soon after apparent recovery she was seized with rheumatic pains, the shoulders swelled and then the wrists and elbows; soon after these the joints of the lower extremities, especially the ankles. She was confined to bed for two months, and went on crutches for four months more. A son of thirteen had, almost at the same time as his mother, a mild dysenteric attack. One month later after his complete recovery the joints of the lower extremity were attacked, the right leg became enormously swelled, and this swelling very slowly subsided. A younger son suffered at the same time from a very severe dysenteric attack, which caused the greatest anxiety. He recovered, however, without complications.

A study of the clinical features of these cases would seem to imply that we have to deal rather with the intermediary infection of the body juices by the poison from the intestinal canal, than with a sudden flooding of the system by the same. The fact that we have no severe general manifestation before the joints are involved would seem further to bear out this assertion. In no reported case has it been mentioned that there were high fever or chill previous to the general symptoms spoken of. The joints are not usually simultaneously involved. One succeeds the other in irregular order, and severity of attack varies with different joints in the same individual. As in the case of post-gonorrhœal arthritis the knee is perhaps more commonly involved. But it by no means is the only joint attacked, and trouble is nearly as frequently met with in the other larger or smaller articulations. According to circumstances we seem to have, in these cases of post-dysenteric arthritis, degrees of severity amounting from simple arthralgia to hydrops-articuli, suppurative synovitis, and complete destruction of the articular surfaces with pyæmic manifestations and death. The effusion when serous or sero-purulent may be trifling in amount, or very extensive. Trousseau states that it may even cause rupture of the capsule. This condition appears seldom to be met with to-day in so severe a form as was described one hundred years ago. Zimmermann states that in Thurgau half the patients succumbed from joint affections, and in Berlin, during the epidemic which Stoll described, there was a large mortality, and pus was frequently found in the joints. In cases reported of so-called post-dysenteric "rheumatism," a fungous, *i. e.*, tuberculous condition of the joints affected has not yet been noted by any author. It is, moreover, surprising that with so many destructive lesions in the joints, so far as I can learn, no instance of serious primary inflammation of bone or of periosteum has been reported. Although pus has been found in so many instances, old and recent, and although Starcke, in 1877, found cocco-bacteria in fluid removed by aspiration from such a joint, I have not been able to learn of any reliable bacteriological study of such a case, and consequently while maintaining the ground that we cannot have pus without bacteria, I am unable to say whether this pus is due to infection from the ordinary pyogenic cocci, or whether a specific or common form of bacterium from the intestinal tract is capable under some circumstances of wandering so far from its proper habitat, and producing pus within the synovial membrane. Certainly between the post-dysenteric and post-gonorrhœal forms of arthritis there is a certain analogy; but as we have already learned that the gonococcus is not a pyogenic organism, and that pus in these instances is produced only by a secondary pyogenic infection, so we may learn later that serous effusion may be caused by the microbe of dysentery, but that pus is produced only as in the other instance.

CHOLERA.

I find but very little literature indicating that cholera is followed by secondary infections. It appears to be too rapid in its course and too violent. Nevertheless, that it is not exempt may appear from the fact that during a recent epidemic of cholera Poulet, of the *Val-de-Grace*, had, in making autopsies, several opportunities to meet with articular and osseous lesions. He found, for instance, in a few, an effusion of fluid, sometimes as thick as molasses, and sometimes of a marked reddish tint. He spoke of it as sometimes resembling opodeloc balsam. Sections of the synovia showed epithelial desquamation with a layer of leucocytes replacing it.

HYDATID CYSTS.

That suppurating hydatid cysts have been accompanied by abscesses in other parts has of course long been known, but whether these be truly metastatic in the ordinary acceptance of the term, or whether their explanation is to be sought for in the usual way, the clinical fact remains—as well as the pathological probability—that these, too, are cases of secondary infection. For instance Verneuil has reported the case of a child with hydatid cyst in the liver, upon which he operated by puncture; shortly after the patient was seized with vague pains about the joints, and a confluent eruption of urticaria.

Later suppurative arthritis was set up about the great toe; violent chills were noted, the abscess was opened and finally the patient recovered. In such a case we certainly have to deal with a purulent infection, and to speak here of rheumatic infection would be simply to misuse terms. Moreover in this case the cyst was not suppurating at the time when it was punctured, although possibly the source of infection may have been introduced with the instrument; but even then to account for so distant an abscess is difficult, although numerous joints were involved in much slighter disturbances. It is known, however, that injection of the most limpid fluid from such cysts gives rise in animals to septic action, and one may well stop, with such a case, to inquire whether resorption of this liquid in Verneuil's case might not have given rise to general infection, with articular localization.

LECTURE IX.

MIXED AND SECONDARY INFECTIONS.

(CONTINUED.)

SYLLABUS.—Infections complicating-pneumonia; Influenza; Measles; Scarlatina; Typhoid fever; Septic angina; Mumps.

PNEUMONIA. Only during the last few years has pneumonia been assigned a place among the septic infectious diseases. This is largely due to Jurgensen. Until very recently there has been some doubt as to which of two or three well-known organisms was really the specific excitant of these cases. But enough has been already said to show that every specific infectious disease is produced by organisms whose general habits and points of attack are well known, but that no part of the body is necessarily or always secure from their invasions. And so it is with pneumonia; while in all probability the coccus with which Fränkel's name is so closely associated is the exciting agent, as shown in Lecture IV, this organism has been known to be the solitary form met with in pus from certain post-pneumonic complications. Such sequelæ of pneumonia have been known for many years. Chomel mentioned some years ago that rheumatism, as he regarded it, frequently followed pneumonia as it did typhoid. Grisolle treated of arthralgias and arthritides of pneumonic patients. In the only one of four cases of extensive joint involvement in which he could make a post-mortem examination, he found the affected joint full of pus.

In 1840 Parise presented to the Anatomical Society the report of a man who, following pneumonia, had what was termed articular rheumatism of both shoulders and one knee; finally one shoulder joint suppurated with the customary local signs and, at the autopsy, there was found also pericarditis with effusion, which had not been recognized during life. About this time also Chomel expressed the opinion that rheumatism not only attacked healthy patients but those suffering from other diseases, like typhoid, pneumonia and especially the various chronic diseases. In 1850 Andral reported, under the name of sub-acute rheumatism, terminating rapidly in death, the case of a woman, æt. 67, convalescing from pneumonia of the lower left lobe, who was seized with violent pain in both shoulder-joints and the right elbow, with swelling and redness of the skin; dying eight or nine days later, pus was found in both shoulder-joints and sero-purulent fluid in the elbow. Nothing was found to betoken a purulent resorption. Gintrac has published a case in which pneumonia, pericarditis and articular abscesses were all met with. At the time those cases were published they were all regarded as of rheumatic origin. Thus Grisolle, writing in 1841 in his treatise on Pneumonia, asks, "What is the nature of these articular pains which I shall describe? Can they be considered as rheumatic, etc.?"

These clinical observations were made in a previous generation, and yet have no small clinical value, for they proved that multiple joint abscesses might complicate pneumonia, and that in the first days of this complication it might be mistaken for a rheumatic affection. In all probability such cases are, strictly speaking, of metastatic origin, and are brought about by well-known embolic lesions. For instance, the section in a case of Jaccoud's showed the following condition of affairs: The right lung in a condition of gray hepatization, beset with numerous small abscesses; the heart gave evidence of a septic endocarditis; in the cortex of the kidneys were numerous miliary abscesses; the right knee and shoulder contained quantities of pus, and near the right shoulder was an abscess in the soft parts which connected with that in the joint. The train of lesions in such a case is not difficult of recognition. Abscesses in the lungs produced endocarditis, and infected emboli from this source caused the abscesses in other parts of the system. The bacteriological investigation of this case was very interesting. In the lungs were found Friedländer's pneumococcus, along with pyogenic forms. These latter were easily recognized in the affected endocardium, and in the peripheral abscesses. They had also been found in a drop of blood taken from the patient before death. This would seem, therefore, to be a true secondary infection by pyogenic cocci according to their well-known capability of action.

Jaccoud, referring to cases of genuine croupous pneumonia which in their course presented pyæmic symptoms, found depots of pus inside the pneumonic infiltrate. In this pus, as well as in that of numerous metastatic abscesses, he has found numerous pyogenic bacteria along with Friedländer's pneumococcus. And two years before Jaccoud Naunyn (*Berl. klin. Woch.*, 1883, No. 29) had called attention to the purulent alveolar contents in cases of croupous pneumonia.

Schüller has reported two cases of monarticular joint abscess immediately following pneumonia, both of which necessitated resection. One such case has happened to myself, the shoulder being the joint involved, the abscess occurring before recovery from pneumonia was complete, perforating the joint, being evacuated by large external incision with counter opening, and so far involving the usefulness of the joint itself as to lead me to advise a resection, which, however, the patient, an elderly man, declined.

Massalonga, in Tregnago, observed an epidemic of pneumonia which was peculiarly severe throughout, and from which the mortality was about 30%. Among the various complications which attracted his attention, articular manifestations, which he called acute articular phlogosis, were quite common, but as a rule were not of severe character. Analysis of various clinical reports makes it appear that post-pneumonic arthritis is usually multiple, although the shoulder is most frequently affected. It may occur early in the disease or during convalescence. The articular lesion is characterized by a burning pain coming on suddenly and spontaneously with exacerbations, and increased by pressure or movement. There is always swelling, sometimes fluctuation, often without superficial redness. A number of times pus has been found when the external appearances would not lead one to suspect its presence. Grisolle has called attention to the marked contrast between the purulent effusion and the condition of the surrounding parts, inasmuch as he met only with a trifling injection of the synovial fringes. Andral also observed nothing but an intense congestion, and Gintrac speaks of nothing but synovial redness. It is seldom under any circumstances that so much pus is observed in a joint with so few evidences of tissue alteration.

In his paper before the German Surgical Congress, before alluded to, Schüller reported the discovery of metastatic joint abscesses in five bodies thus dying from pneumonia. He carefully examined the pus from all these and recognized streptococci, as well as pneumonococci of Friedländer. There appear to have been no instances of post-pneumonic bone abscess reported, nor has the writer anything to add on this subject except that, reasoning from analogy, it would appear to be strange that their occurrence has not yet been noted, and that it need surprise no one should their occurrence be described at any time. As a matter of interest, yet not bearing directly on the present subject, it is worth while to remark that myalgias and arthralgias have been described by at least two different writers as causing a very unpleasant or distressing feature of pneumonia.

Gabbi has endeavored to produce experimentally a suppurative arthritis by injecting Fraenkel's diplococcus into the joint cavities of rabbits. When he combined the injection with mechanical irritation he got unmistakable disturbance; but the simple injection of the coccus produced only a seropurulent exudate.

Monti studied the exudate from a case of arthritis which developed in the wrist of a patient suffering from double pneumonia along with pleuro-pericarditis, and found a pure culture of the diplo-coccus. Belfonti had a quite analogous case, involving also the wrist, which he studied with the same result. He regarded the localization of the joint lesion as an instance of mycotic embolism due to specific endocarditis. These cases serve as a further illustration of the pyogenic power of Fraenkel's coccus.

Acute meningitis is known to be caused sometimes by this diplococcus, even though the patient at the time is not suffering from active pneumonia.

A recently reported case, of Fraenkel's, is a most interesting confirmation of this fact. A man, æt. 32, shot himself in the left temporal region; there were no brain symptoms, and the external wound closed promptly. In twenty-one days he seemed completely well. At this time he was suddenly taken with a severe chill, followed by serious symptoms, and death ensued in five days. At the autopsy a collection of puruloid material was found between the dura and the supra-orbital plate of the frontal and beneath it. Cultures of it, as well as from various parts of the intensely congested brain, from the ventricular fluid, and from blood from other parts of the body, showed it to be a case of septic infection from the diplococcus pneumoniæ. This organism in all probability gained aceess from the nose, which would seem to indicate that careful disinfection of the nasal cavity is advisable in those injuries to the bones of the skull where direct or indirect connection with these cavities may occur.

In parenthesis it may be stated that the paths of lymphatic conduction have been recently clearly traced from the nasal mucous membrane into the brain itself, and an explanation for certain brain abscesses is afforded by this statement of anatomical fact. A most interesting case lately under my own observation is one of frontal abscess following an operation for the removal of nasal polypi. At another time and place I shall report it in greater detail.

Testi has reported a case of double-sided parotitis which developed in the course of a case of croupous pneumonia, in which he found Fraenkel's diplococcus. This organism was also found in the pus from the pleura, as well as in that of several superficial abscesses from which the same individual also suffered. Gabbi has studied some of these secondary lesions and regards the tonsils as playing a considerable *rôle* in some of them. In the ulcerated follicles, as well as in other parts of the body, he found the pneumococcus of Fraenkel, and along with it, in the tonsils, the staphylococcus aureus; both were also found in the saliva.

Zaufal has recognized the pneumococcus in the purulent discharge from six cases of otitis. He reports seven further cases of pneumo-diplococcus otitis, four of them complicated with mastoid abscesses, which were all caused by this same organism. Levy and Schrader have investigated fourteen cases of acute and two of chronic suppuration of the middle ear; in several of them the diplococcus was found.

Verneuil claims to have found Fraenkel's coccus in the pus of a subperiosteal mastoid abscess which resulted from an otitis media, and which latter was the result of an operation on the nose. It is reported also that Netter found the pneumo-coccus not less than thirty-five times out of seventy-five cases of otitis media studied.

INFLUENZA.

The pandemic character of the spread of *la grippe* a year and a half ago caused the most intense interest in its character and pathology. Not alone to physicians was this a matter of importance, but to surgeons as well, since there resulted from it not a few cases which sooner or later came into their hands for treatment. Although I know of no satisfactory and definite conclusions as to its nature, I have seen more than one of its surgical sequelæ.

It is well known that a disease of a similar character has been epidemic among animals, especially among horses, and that inflammations of joints are a frequent complication of these cases. Indeed, upon the continent, cavalry garrisons have been almost disabled or placed *hors du combat* by reason of this, consequently it would be an oversight not to mention it among the diseases under consideration in this lecture. Arthralgias have been very common. A true serous synovitis occurs occasionally, while more destructive forms seem less known. Witzel describes, for instance, a case of severe periostitis of the tibia, and calls attention to the similarity between this case and similar cases occurring after typhoid. He describes also a similar case involving the lower portion of the femur, in the person of a little child. He alludes also to the occurrence of necrosis as well as to the frequency of later fungus inflammations of bones and joints. At least one case of pyarthrosis, mainly of the knee, occurred under his observation, and he alludes to the fact that in the sero-purulent fluid from such a joint Ribbert had discovered streptococci. Evidently, then, la grippe is not a disease which surgeons can afford to completely neglect.

Within a week I have had to open a large subfascial abscess of the thigh, evacuating nearly a litre of pus, which made its appearance while the patient, a man of 31, was recovering from the acute stage of the grippe. He had been previously well, and had not injured himself, so far as known.

In a recent number of the Bulletin of the Academy of Medicine, an article by Verneuil shows that the influenza has been followed by a relatively large number of sequelæ, whose main pathological feature is suppuration. He has observed suppurative infections of the eye, ear, joints, pleura and pericardium, as well as superficial and deep abscesses of the skin and glands, and collections of pus in the antrum and the frontal sinus. These were treated by proper surgical measures, but seemed more rebellious than do similar lesions under ordinary circumstances. All of which is to be explained probably by the marked depreciation of the patient's general health. He also observed that patients who were in the stage of recovery from operations, when attacked by the grip, suffered from complications which were often serious. This fact was also noted by Walther of the Charité Hospital, who observed a remarkable slowness of the healing processes under the same circumstances. Cicatrization was retarded and not re-established until after complete cessation of the acute febrile symptoms.

Demons, of Bordeaux, mentions quite a number of surgical complications of the grip under his observation. Otitis complicated with mastoid abscess, severe inflammations of the eye, acute orchitis, and other equally severe lesions occured several times. He also saw formation of abscess in the axillary glands as well as elsewhere, although none of the ordinary causes of suppuration could be found. He furthermore states that in all wounds in his wards, healing was slow and suppuration profuse. According to his opinion, during an epidemic of the grippe it is most wise to abstain from all operative procedures, and especially those involving the nasal, buccal, pharyngeal and respiratory tracts, which are especially liable to be attacked by the disease. Evidently then the prognosis of operations performed during an influenza is a matter carefully to be considered, and the wisdom of postponement of all operations, not immediately necessary, until the patient has recovered from the debilitating effects of the disease, is most apparent.

MEASLES.

Concerning the relation between measles and consecutive suppurative lesion, there is but little to be found in literature. Demme observed two cases of acute osteo-myelitis consecutive to measles, one a 5 year old girl who developed an abscess in the upper end of the tibia, which was opened on the 6th day after the disappearance of the eruption. She recovered. Another girl, æt. 9, five weeks after the disappearance of the exanthem, developed an abscess in the lower end of the tibia, accompanied by chills, nausea and high fever. This evacuated itself spontaneously eleven days later, and in a month she was well. It must be said of the latter case, however, that it is uncertain whether it should be put in this catagory, or was not in effect a purely idiopathic affection.

Luecke lays special stress upon measles in discussing ætiology of bone and joint diseases. He emphasizes that in the course of the disease, and especially during convalescence, the bones and joints were frequently seats of affection, and that it has been known in all ages that children who have suffered from measles very often quickly develop the so-called scrofulous appearances, which are not confined to the glands and skin alone, but frequently affect these deeper parts; and Witzel, in commenting upon the above statement, states that he knows of no one of the diseases of children which appears to furnish so favorable soil for tuberculous processes as this, stating that scarcely a week passes without the appearance of some patient whose fungus inflammation has developed shortly after measles. (Gibney, *Med. Rec.*, June 3, 1882.)

In 1845, Bonnet in his treatise called attention to the fact that in the eruptive fevers which have pursued a somewhat irregular course, when the eruption is incomplete there appear often pain and disseminated inflammation about the various joints. In 1865, Marjolin presented to the Surgical Society the femur of a young child dying of measles, which presented all the symptoms of coxitis. Two similar cases are also spoken of by Vallette. During the same year there was a notable discussion in the French Society of Surgery concerning coxalgia, in which Verneuil claimed that measles could not be a direct cause of arthritis, but only so far as it quickly reduced the general condition of health. Ollier held that cold was largely to blame for these lesions, and that all forms of diathesis secondary to fevers appeared to be the result of the susceptibility to cold which all convalescents alike manifest. Matthieu and Strauss would explain these lesions by a tendency to hyperæmia common to all grave febrile conditions. Martin and Collineau regarded hyperinosis as playing an important rôle in the production of these complications. Follin and Duplay consider that the common suppurative arthritis might develop alone under the influence of the general enfeeblement of the constitution by which a peculiar susceptibility to external causes and especially cold was produced.

Measles and scarlatina have, in this matter of liability to secondary infection, so much in common, that it would appear proper to consider them together.

SCARLATINA.

Scarlatina must be recognized as another of the acute infectious diseases, during the occurrence of which suppurative complications may arise. As in the case of diphtheria, to be mentioned, the tonsils and other adenoid tissues are so universally and so early involved that a ready and easy path of infection is afforded. This specific fever bears some resemblance to dysentery in this respect, that sympathetic infection of serous membrane occurs very often while the occurence of ostitis postscalatinosa is rare. It must be said, however, that tubercular joint and bone complications, as well as those of glands, are very common after these diseases, as a careful study of accurate histories of tubercular cases will invariably show. As was mentioned when considering dysentery, there appear to have been at different times epidemics of scarlatina during which serous or suppurative joint complications were very frequent. For instance, Kennedy, writing in 1843 of an endemic which prevailed in Dublin from 1834 to 1842, spoke of the frequency and malignancy of this complication. Sometimes a single joint was involved, often three or four of the larger joints filled up with pus, and sometimes even there occurred epiphyseal separation.

In these cases, at least as he described them, the internal organs revealed few, if any, changes.

But to show that this is at least unusual, Bonnet, in his classical work on the joints, stated that the rheumatic complications following scarlatina manifest no tendency toward pus formation, in which respect they were very different from those occurring during or after small-pox. According to Betz, who wrote in 1851, synovial complications of scarlatina were very common, the serous membranes being more or less affected. He took the ground that the implication of the synovia preceded the appearance of the eruption, and was not to be regarded as a secondary manifestation.

Trousseau was the next prominent writer to discuss this complication, which he constantly spoke of as a rheumatism. He described the rheumatic diathesis as affording the explanation to the condition, and said that it involved first the joint, and later the serous membranes like the periosteum and the pleura. Furthermore that it sometimes assumed the most dangerous form, viz., the suppurative, which he likened to the similar condition following the puerperal state. According to Koren, so-called rheumatoid complications of scarlatina occur in six per cent of cases. Ashby twice saw joint abscesses among five hundred cases of the fever. Post scarlatinal arthralgia appears to be not uncommon. The true arthritis appears to begin in the second or early part of the third week, only exceptionally earlier. A simultaneous implication of tendon sheaths and bursæ has been noted in some cases.

The ordinary form of arthritis appears as a small hypersecretion of synovial fluid, and the joint may remain sensitive for a long time. It is even possible for the capsule to become so distended that a chronic hydrops results with more or less of flail-joint. Güterbock once saw spontaneous dislocation of the hip in a seven-year-old girl from this cause alone without the presence of pus, and I have seen the same thing. A contrary condition of affairs is sometimes the result of the changes mentioned above. By a combination of hyperplastic thickening of the synovial membrane, along with contraction, there is brought about a shrinkage of the capsule and a fixation of the joint, sometimes in a most undesirable position. I have had, for instance, under my observation, at least two cases of young girls whose knees were almost rigidly fixed in position near a right angle, as result of changes of this kind consecutive to scarlatina. For one of these nothing could be done; the other required open division of all the soft parts excepting vessels and nerves, and including the ligaments, down to the joint.

Trousseau, in speaking of the rheumatic or rheumatoid complications of scarlatina, with propriety assigns them a middle ground, as being less serious than those consecutive to typhoid, dysentery and gonorrhœa; but it is unquestionable that primary suppuration does sometimes occur in these joints, which naturally leads to the query whether the scarlatinal poison can give rise to pus. Just what this specific agent is we are not yet certain, consequently do not know whether to regard these cases as secondary or mixed infections. So far as I can learn in such pus none but the ordinary pyogenic cocci have been recognized.

This infection, whether secondary or mixed, is certainly at times excessively rapid. Trousseau relates a case of a young girl seized on one day with extremely severe symptoms, whose wrist was already swollen, red and painful on the second day; on the third day both wrists, a shoulder, a knee and an ankle were involved, and a blowing murmur was heard over the heart; on the fourth day the condition was in every respect worse, fever was high and on the next morning the child died. No noteworthy lesions were found in the internal organs, but all the joints which had been involved were filled with greenish yellow pus. This cannot be regarded as a pyæmic case, but means rather that the multiple joint abscesses can be caused by some scarlatinal mixed virus acting directly. In this case the disease began with a severe angina, as did it also in both of Ashby's cases. This is of interest in connection with Löffler's experiences. He cultivated streptococci from the false membrane of a case of diphtheritic scarlatiniform angina, pure cultures of which, when injected into the circulation, caused multiple joint abscesses, from which again the same cocci could be recovered. Various clinical features appear to make it evident that the pyogenic infection which complicates scarlatina is not directly connected with it. Penetration of pyogenic cocci would seem to proceed through the affected pharyngeal tissues. This has been especially insisted upon by Bokai. In this respect then diphtheria and scarlatina stand together, as affording excellent opportunity for penetration into the body tissues and juices of pyogenic organisms through the same parts which are so severely involved. Heubner has described a case of this kind in a fourteen-year-old boy, one of whose knuckle-joints was first involved, later the knee, then the other hand, then both lower extremities became œdematous. The autopsy revealed purulent infiltration back of the right tonsil, and an extensive phlegmonous process in that side of the neck, which had extended to the right jugular vein and produced an extensive thrombo-phebitis. There was also fresh pericarditis. The joints involved were extensively disorganized. In the pus and in the blood were found Löffler's organisms. Such a case as this shows how peripheral abscesses may occur pretty directly without necessary intervention of the lungs, since Löffler's experiment showed how they might involve the joints directly from the circulating blood.

However it is not only for the favorable reception of pyogenic cocci that the virus of scarlatina prepares the joints, but equally well for the disposition and growth of tubercle bacilli. Volkmann, Bokai and others have shown how directly scarlatina appears to lead to fungous complications in the joints, especially of the non-articular form. This occurs with especial ease in children with inherited or acquired scrofulous diathesis, in whom apparently it needs only the impression of the specific virus to call out whatever latent tendencies they are capable of exhibiting. So far as bone inflammations are concerned there should be mentioned in this connection especially the partial necrosis of the alveolar process, which Salter has so fully described under the term exanthematous jaw necrosis, which he met with as well after measles and small-pox. It affects children between the third and eighth years, and begins with pains in the jaws a few weeks after apparent recovery from scarlatina. Along with discharge of badly smelling pus a portion of gum separates, and with it one or more teeth so that the alveolar border is exposed, to be itself exfoliated a little later. According to Thomas, a similar condition of affairs takes place beneath the periosteum of other bones, the manifestations varying very much in time and intensity, appearing to be due to an exudation beneath the periosteum and its subsequent breaking down.

Indeed, he regards the majority of cases of necrosis in early childhood as due to an earlier attack of scarlatina. It appears, however, that he does not appreciate the frequency of tubercular secondary infection, and the fact that most cases of necrosis are expressions of this condition. The many instances of disease of the bone, in connection with affection of the middle ear, consecutive to scarlatina, would appear also to be of this same general character. Betz has found extensive purulent destruction of the ribs at various points. Kennedy has described epiphyseal separation. Graves has seen Pott's disease of the cervical spine, and Hauff and Hamburger have observed it in other bones. In his work on General Surgery Fischer has stated that during the course of scarlatina and small pox he had observed the most acute and serious form of inflammation in the bones of the foot, with formation of a fluctuating tumor, inside of which these bones lay almost completely loosened from their periosteal and other connections. He lost three young patients from trouble of this kind inside of eight to fourteen days. Of course, this is not to be regarded as the direct effect of scarlatina, but rather as brought about by a secondary pyogenic infection. In general we wish to emphasize that most of the cases of necrosis ascribed to scarlatinal poison are really the result of a fungous ostitis, usually of tubercular character, with consequent caries or necrosis, the whole being due to easy secondary infection with tubercle bacilli in ground already poisoned and prepared by the scarlatinal virus.

Barwell, speaking of the joint complications of the exanthematous diseases, says: "These affections have often, like gonorrhœal joint maladies, been ascribed to rheumatism, even have been termed consecutive rheumatism; but the only point in their course and condition which at all resembles the rheumatic, is that they are nearly always multiple; they possess neither the temperature of rheumatism, nor the slightest tendency to involve the membranes of the heart or brain."

Barwell states the case about as follows: "The joint affection following scarlatina tends more often to the suppurative form, and to produce, if the attack be at all severe, either disorganization or anchylosis very rapidly. The synovitis which follows measles is, more than any other of these secondary inflammations, inclined to fall into the chronic phase after a subacute attack of a few days, and then to give rise to or become changed into strumous synovitis. This tendency of strumous inflammations to follow measles is not confined to joints, but may also be observed with regard to cervical lymphatic glands, palpebral conjunctiva, auditory meatus, etc." * * * "But sometimes an exanthematous synovitis is empyæmic and patients die of such disease consecutive to one of the skin fevers, and then the joint affection, considered merely as a symptom, is barely mentioned. Such mortality only occurs when the pristine malady leaves behind it some suppurative focus, such as pharyngeal ulcer from scarlatina, measles or typhoid, one or two obstinate sores after small-pox, suppuration of the parotid after mumps, a meso-rectal or meso-colic abscess after dysentery, etc. Here the origin of the infection continuing, the infection itself goes on. Another, a monarticular form, is likewise said to occur as a sequel to exanthemata or to dysentery. This, however, must be extremely rare for all such diseases. I have never seen a case of exanthematous synovitis commencing in a single joint."

Three pretty distinct forms of severe complications of scarlatina have been distinguished: *a*, Common acute serous arthritis, which has often been spoken of as a scarlatinal rheumatism; *b*, a serous arthritis which passes into a suppurative form, and *c*, arthritis which is purulent from the beginning, and is accompanied by the ordinary phenomena of purulent infection. The first form appears usually at the end of the second week, or at or about the period of desquamation; but few joints are involved, the wrist most commonly, and next the knees and ankles. Graves has reported four cases of localization in the joints of the cervical vertebræ. Pains, sensitiveness and swelling are moderate. Bokai has described a subacute form which often leads directly to white swelling, but he thinks, andwith reason, that the scrofulous diathesis predisposes to this condition. The second form is regarded by Kennedy Corrigan and others as the more frequent. It begins usually as a small polyarthritis whose attending symptoms, such as fever and swelling, increase in severity as the serous fluid is transformed into purulent. According to Bokai this disease terminates most often in death, or when patients recover they are usually found to have anchylosis of the affected joints. The third form is hardly peculiar to scarlatina, but is met with in various severe infectious diseases. Hebra and Kaposi have described rare cases of purulent arthritis produced by perforation of peri-articular abscesses, and latter these writers have considered these as due to embolic processes, such as are common to phlegmons of the neck, thrombosis in the cervical veins, gangrene of the pharynx, etc. This form is almost invariably fatal.

Babes ("Concerning Septic Processes in Children") has made a most important contribution to the subject of mixed infection. His researches are based upon systematic bacteriological investigation of the material from 112 autopsies on children. The majority of cases were of a septic character following scarlatina, diphtheria or external injuries. The existing agents of the septic infections appear to be less often individual forms than a mixture of two or more species.

Among these the pyogenic and the saprogenic forms were, of course, most common. The latter frequently resembling those from the intestine, appeared to have penetrated into the tissues, and to have there displayed pathological activities. A third group of these forms was constituted by those peculiarly septic bacteria in the sense in which Koch has described them. Babes has succeeded in cultivating not less than eight of these species (among them the rabbit-septicæmia bacillus of Koch) from the organs of children dying from septicæmia. Of particular importance is Babes' view concerning the relations of streptococcus pyogenes to scarlatina. This disease is, according to his view, always accompanied by these cocci, and, indeed, the whole scarlatiniform process may be regarded as a modified streptococcus infection. The nephritis in scarlatina, for instance, would thus appear to be an invasion of this organ, since it is almost constantly found in the affected kidneys. It is of peculiar interest in this connection to realize that the cocci cultivated from the less acute or more chronic forms of scarlatina evince much less violent activities than those recovered from the more rapidly fatal cases. In other words, they appear to have a lesser degree of virulence after cultivation on artificial media.

Babes separated a streptococcus septicus liquefians from putrid bronchitis and pulmonary gangrene after scarlet fever, as well as one corresponding to Hauser's proteus, which he found in the lymph spaces of the mucous membrane in a case of dysentery.

Marie Raskin has found streptococci in numerous cases where abscesses have complicated scarlatina. The pus from these abscesses as well as from the joints was often almost a pure culture of this organism, while in pus from the middle ear, staphylococci and streptococci were mixed. Streptococci were twice found in the blood of living patients, and twice in that from the cadaver. In 64 cases uncomplicated with suppuration, no streptococci were found in the blood. Twice out of 18 cases examined streptococci were found in the skin and in the desquamated scales. She comes to the conclusion that streptococci are the active agents in secondary purulent infection after scarlatina; but that they have nothing to do with the fever itself. She concludes further that the inflamed tissues in the throat are the ports of entry for these infective agents. (*Ctrbl. f. Bact.*, V, 1889, p. 286).

Lenhartz found in a severe case of scarlatina, accompanied by abscesses in the neck and joints, as well as by a diphtheritic condition of the pharynx, a streptococcus, which by experiment upon animals he identified as the streptococcus of erysipelas. (This has been already shown to be identical with the streptococcus pyogenes). He too regards the pharyngeal mucous membrane as the port of entry, and in this case the intense inflammation which it showed he considers to be a modified erysipelas of the mucous membrane; Heubner having already described a genuine erysipelas of the face following scarlatina and diphtheria of childhood. (*Jahrb. f. Kinderheilk.*, Bd. 27, 1888).

TYPHOID.

Although in such masterly works as those by Liebermeister and Murchison, joint and bone complications find no mention as sequels of typhoid, they have long been recognized by surgeons. The names of some of the most eminent surgical writers are connected with the study of typhoid and post-typhoid articular lesions. Boyer, for instance, observed spontaneous dislocation of both thighs after an "essential fever." Post-typhoid hip dislocations have also been reported by Roeser and Stromeyer, by Hueter and Volkmann. The matter of spontaneous luxation and other joint affections subsequent to typhoid, was prominently brought before the Congress of German Surgeons by Gütterbock. While these serious joint disturbances are fortunately rare, some men of large experience having never seen one, they are, nevertheless, common and serious enough to demand recognition, and they have moreover most interesting pathological features. Strange to say, so-called rheumatic affections of joints occur very much less often after typhoid than after dysentery. Still I am sure that many practitioners can recall patients who have entirely recovered from typhoid, who have yet complained of more or less painful joints for some time after. Several of the French writers have recognized this in the terms typhoid arthralgia and myodynia. It is scarcely necessary to say that a true combination of rheumatism and typhoid occurring simultaneously, is scarcely or not at all to be thought of. Secondly, there is underlying the term post-typhoidal rheumatism, such an impossible condition of affairs as to forbid its use or that of anything equivalent to it. That the mistake is usually made, such a case as the following, quoted by Gütterbock from a report of Simons, will indicate: A patient, æt. 19, suffered from swelling of both ankles, and was supposed to have a severe form of acute rheumatism; not until after due recognition of a typical temperature curve and enlargement of the spleen, and of petechiæ, was it discovered that he was in reality suffering from typhoid fever, and that the joint swellings were merely an unusual manifestation of the typhoid poison.

It is somewhat *singular* that when such serous effusions as those into the pleura and pericardium are generally recognized as possible complications of this disease they should be regarded as so occult when they occur in synovial cavities. Volkmann and Keen have alluded to a polyarticular form of the same condition, which we may call post-typhoidal serous arthritis. Multiple joint abscesses have been more rarely seen, and when present have generally led to or been connected with the pyæmic condition. Nevertheless Gütterbock has reported the following case of recovery from this most serious condition: A young woman was admitted to the hospital at the end of the second week of the typhoid fever, which had been of only moderate severity. During the fourth week there was a hypostatic pneumonia with bloody sputum, and then for several days she had repeated chills. During these there occurred an acute painful swelling of the left shoulder, which improved under the application of ice. The chills continued, and two days later the left hip was similarly affected. Two days later the chills ceased, and she slowly recovered.

A case of Robin's shows how pus may be collected not only in the joints, but in the tendon sheaths and bursæ, as well as in the cellular tissue at some distance. Doubtless such a case as this implies mixed infection, the primary infection being by typhoid bacilli, the second with pyogenic cocci.

Investigations of Brieger and Ehrlich concerning the relation of malignant œdema to typhoid have shown very plainly that various bacteria, which in the healthy body would produce no disturbance at all, find a more or less unresisting organism in the individual whose vitality has been lowered by an attack of typhoid fever. It is not difficult to see then how pyogenic bacteria may penetrate through the intestinal walls or by the air passages, or from the tonsils or teeth, without meeting with that resistance which they would surely encounter in the healthy body. Thus they allude to streptococci which they found in an abscess produced by breaking down of an axillary lymph gland during the course of a fever. According to Brieger, suppurations during the course of typhoid are rare, but Dunin claims to have found them in a fourth of all his patients. He found the pyogenic cocci in all of the cases which he studied, and regards the ulcerated and necrotic patches in the intestinal canal as their port of entry. With everything so predisposing to metastatic infection and pyæmic condition, it is very strange that it has not been more often met with.

Post-typhoidal monarthritis as well as polyarthritis possess great interest for the surgeon, especially when they may run so severe and destructive a course as to lead to spontaneous luxation. One may easily see, indeed, how this subject may possess a medico-legal interest, since, if it occur in a patient already maniacal or delirious, it might lead to supposition of violence on the part of the attendant, which would have nothing to justify it. In fact Schotten has reported a case where such a dislocation occurred while a nurse was raising a child. The best exposition of this part of the subject was made by Roeser, in 1857, who ascribes it principally to distention of the capsule by a fluid effusion from within. In a patient of Stromeyer's, æt. 61, the capsule of the hip-joint was so distended that fluctuation could be easily recognized in the groin. When these dislocations have spontaneously occurred they have usually been at the hip. Very rarely the shoulder has suffered. In fact I believe there are but two such cases on record, one by Meyerhoff, the other by Keen. Keen also has reported one such dislocation at the knee. It is usually the monarticular form which ends in suppuration, and it is quite possible for functional recovery to occur when such an empyema of the joint is radically treated by incision, irrigation and drainage. In the pus from such a joint typhoid bacilli are sometimes found, but most commonly the ordinary pyogenic forms alone. That more extensive destruction than that of the capsule may take place is illustrated by the case of Weil, in which there occurred not only suppurative coxitis, but a separation of the upper margin of the acetabulum, with, of course, consecutive dislocation of the hip. Fortunately in this case a very useful joint was secured by treatment with traction; which justifies an observation of Bell's that a complication of dislocation with suppuration in the joint was favorable rather than unfavorable.

In 1878 Robin reported a very interesting case of adynamic typhoid fever in which on the eighth day there rapidly supervened a purulent synovitis of tendon sheaths, of multiple periostitis, and finally of suppurative synovitis involving numerous joints. The patient succumbed on the twenty-third day.

It is mostly toward spontaneous dislocation that the non-fatal cases of suppurative arthritis tend. Out of forty-three cases Keen met with thirty spontaneous luxations, twenty-seven of these in the hip, two in the shoulder and one in the knee. Roser was of the opinion that a large proportion of spontaneous luxations in children which were considered as due to rheumatic affections were really of typhoid origin, and Lannelongue has reported three new cases corroborating this view.

The phenomena which precede the occurrence of luxation are variable; for the most part they are symptoms of intense arthritis. On the other hand it does not seem essential that a large amount of effusion should first occur. The explanation of which fact is simple if we admit that the intensity of the disease occurs in the epiphysis and not in the joint. Especially is this the case at the hip when the acetabular side of the joint is involved, and if true, this will explain the difficulty or virtually the impossibility of permanently reducing these dislocations, since, as mentioned by Keen and others, they are almost impossible of retention in place.

So far as suppurative lesions in the bones are concerned, our knowledge is very much more recent. Indeed this is almost a matter of the last ten or fifteen years.

Konig mentions in his text-book that he has often seen small abscess in the tibia after typhoid. In a dissertation published in Zurich in 1868, Cerenville mentions inflammation of bone as a sequel. In 1872 Meusel operated with success upon a necrosis of the skull consecutive to typhoid. Paget's papers in 1877 and 1878 were a valuable contribution to the subject. But perhaps the most elaborate paper on the subject came from the pen of Dr. Keen in 1878, who collected thirty-nine cases; but the explanation which he put forward, of thrombosis or of occasional embolism, must lose a part of its force and attractiveness in the light of the bacteriological knowledge of to-day. Still later a French military surgeon, Mercier, brought forward a dozen new cases of bone inflammation during typhoid without the occurrence of sequestra such as Keen had reported. Since then numerous observations have been made by Levesque, Ronda, Gelez, Turgis, Hutinel and Terrillon, and the writer has added his mite to the same subject.

Inasmuch as this topic has been of late carefully studied in its biological aspects we may now say that there is no such thing as post-typhoidal rheumatic affection of bone or joint, but all such cases are to be ranked either as primary or mixed infections, whether occurring in bone or joint cavities, and that while in a few instances the pus therefrom has been found to be almost a pure culture of typhoid bacilli the majority of these cases are genuine mixed infections. With the occurrence of these suppurative foci in these particular structures we must not forget how often they may occur in other parts of the body where they are better concealed or less suspected; and this leads us to the observation, in parenthesis, that no small proportion of patients dying from typhoid fever undoubtedly perish from the presence of collections of pus which, not being recognized, lead to a fatal result by ordinary septic processes. It is scarcely necessary to rehearse in detail the now numerous cases of sub-periosteal, intra-osteal and intra-articular abscesses following typhoid, whose pus has been carefully studied, and in which typhoid bacilli have been recognized.

Barwell (Chapter IV of his "Treatise on Diseases of Joints") mentions that one of his colleagues, Bellamy, had to excise the hip of a boy, æt. 11, who had suppuration of that joint occurring in the course of a typhoid fever. Barwell further alludes to two different forms of joint abscess; one, which is mostly confined to the hip, is intra-articular, and produces rapid effusion and dislocation. It is usually so painless, or the patient is so apathetic, that the condition is not infrequently recognized only when the patient is convalescent and about to quit the bed, when luxation becomes evident. "The other form is multiple, begins toward the end of the second week, and occasions more suffering; tenderness and pain on movement are especially strongly developed; the swelling is marked by considerable cutaneous redness and peri-articular abscess threatens constantly, yet may disappear; œdema of parts beneath the inflamed parts is strongly accentuated."

All that has been said in previous lectures concerning the peculiar predisposition which the anatomical structure of these parts affords with reference to acute osteo-myelitis, etc., will apply equally well here. The arrangement of the deeper periosteal layer, and the proximity of the epiphyses, have their inviting effect.

Statistics show that in at least two-thirds of these cases individuals are affected during adolescence or in early childhood. Undoubtedly, then, we have to seek for the predisposing causes in the nature of the osseous tissue itself, and we shall find it, as in the case of acute osteomyelitis, very favorably predisposed. It is an accurate general statement to say that during the period of active growth, the very lively circulatory activity of the deeper periosteal layer, and the neighborhood of epiphyseal junctions, predispose to this form of local specific infection. Typhoid fever appears to bear a peculiar relation to the growth of the bone, since it has been noticed that during typhoid fever or after convalescence, there has been an extraordinarily *rapid growth in length, as much even as* *one mm. a day.* This is most probably caused by the irritation of the typhoid poison upon the osteogenetic tissue.

In this connection, also, it will be remembered that convalescents suffer from peculiarly active and frequent "growing pains," with frequently a marked tenderness upon pressure in the bones involved. Furthermore, Ponfick, Litten, Orth and Gosselin, have found, in the bone marrow of those dying of typhoid, hyperæmic areas at the points above mentioned, which were almost inflammatory in appearance. Therefore, it is not strange that at these points invasion of infecting bacteria may be most marked, or that when they are thus involved a second pyogenic infection is much easier. This mixed infection must necessarily always lead to abscess formation; but these abscesses are not necessarily confined to bones or joints. Schede (*Munch. Med. Woch.*, 1888, No. 11) has called attention to the suppurations which occur during and after typhoid, in the glands, muscles and in goitrous enlargements, as well as in the osseous system. During one epidemic he saw ten cases of bone abscess; two of these were in the mastoid process, two in the humerus. In the pus from these abscesses he found always pyogenic cocci, but never typhoid bacilli. Several others have shown that recidive of suppurative trouble may occur. They have also shown that the head of the tibia is the most common site of such trouble. Another very curious feature of this subject is that upon which Witzel has laid considerable stress. He calls attention to the relative infrequency of these complications until within a few years; also to the fact that within the past few years the treatment by baths has been much more widely adopted, and he queries whether injuries to the limbs of the patient upon the sides or edges of the bath-tubs, or the sides of the beds, may not have considerable to do with their origin. Such injuries are naturally very slight, but he thinks the irritation may be sufficient to produce a deep abscess.

When these post-typhoidal complications occur, they are much more often acute than chronic. It is possible to have a very acute non-suppurative form of post-typhoidal periostitis, as a case in the writer's practice will show.

This was a young lad of 14, who developed a most intense and painful multiple periostitis during the end of the third week of an ordinary attack of enteric fever. He recovered finally. All the bones of both lower limbs, as well as the pelvis and several vertebræ, were involved.

But a long persisting thickening of the periosteum is very rare.

With reference to the discovery of typhoid bacilli in pus from these sources, it is well to recall what Eberth himself said about their frequency. As a matter of fact the bacilli are most numerous during the first twelve days of the disease, and from that time till the end of the third week they diminish quite rapidly in numbers, and during the fifth and sixth weeks they are only exceptionally to be found. Ebermaier's discovery of quantities of typhoid bacilli in apparently healthy bones of typhoid patients, and especially in a non suppurative periosteal swelling in the same cases, is of very great importance, especially in connection with such instances as that above reported by myself. This author alludes to the similarity in tissue and function between the spleen and bone marrow, and regards it as not at all strange that the bacilli are frequently to be found in the latter. He also succeeded twice in finding the bacilli after incision into a so-called rheumatoid swelling of the periosteum. Such discoveries as this must serve as corroborative evidence of the position taken in Lecture IV, that typhoid bacilli may at times have pyogenic activities, but are not to be regarded as belonging in the obligate pyogenic group of micro-organisms.

It is no harder to think of secondary infection with pyogenic organisms, as the true cause of most of the suppurations met with as post-typhoidal complications, than it is to regard them as secondary but active agents in causing most abscesses in tubercular tissue or in syphilitic gummata. There is another class of lesions met with in these cases where there forms a collection of broken down puruloid material. This must often at least, if not always, in the absence of other organisms, be regarded as the product of a retrogressive metamorphosis, or degeneration of cell elements thrown out to protect against the typhoid bacilli. This form of lesion is frequently met with between periosteum and bone, and it is in such instances that the bacilli in question occasionally manifest pyogenic activity. A clearer recognition of the occurrence and clinical course of these complications would enable one to properly catalogue them, and not be at a loss to account, for instance, for what must, at first, appear to be an idiopathic acute osteomyelitis as a sequel of a severe zymotic disease.

But there is so much to be said in this matter concerning typhoid alone that, to make such an essay reasonably complete would take more than two whole lectures. I must, therefore, fall back on my expressed intention of being suggestive only in this rehearsal, and consequently desire to bring together a few observations of widely scattered investigators, all of which point in the same general direction. Take, for instance, the fact reported in the *Deutsche Med. Woch.* for 1890, No. 48, p. 1086, where it is shown how typhoid bacilli have been found alive in the tissues and capable of active growth *seven months* after cessation of the fever.

The investigations of Senger, too, will help to explain mixed infection after typhoid. A patient died of a post-typhoidal, acute, varicose endocarditis. In the lesions on the heart valves there were found no typhoid bacilli, but quantities of streptococci, which latter were also found in the swollen mesenteric glands. Senger regarded the intestinal ulcers as the ports of entry for the streptococcus infection, remembering that such invasion of typhoidal ulcers by pyogenic and other cocci has been often met with, and that Gaffky has found them often in the mesenteric glands, and in one instance in various internal organs.

Fraenkel accepts without reserve this possibility of secondary infection, and found in one case the spleen swarming with "pneumonie-ahnlicher" cocci, which were extremely pathogenic in guinea-pigs. The invasion occurred after the formation of dysenteric ulcers resulting from abuse of calomel.

Rheiner observed, in Zurich, during the typhoid epidemic of 1884, six cases of erysipelas during the course of the typhoid. Two of these were fatal. In the erysipelatous skin typhoid bacilli were also found.

Foá and Bordoni-Uffreduzzi found almost pure cultures of typhoid bacilli in the lung juices from the hepatized lung of a typhoid patient dying with croupous pneumonia.

Klebs found typhoid bacilli in the purulent exudate from the pia in a case of cerebral complication of typhoid.

Dunin had numerous opportunities to observe suppuration and phlegmons in various parts of the body after typhoid. He found only pyogenic cocci, and considered that they had invaded the tissues *via* the alimentary canal.

Ponfick found in the bone marrow of many patients dying of typhoid numerous changes, and Freund has concluded when the bone is thus involved, as a sequel to the fever, that the affection has its origin in the marrow and subsequently spreads to the periosteum. It is likely also that the joint pains of which many of these patients complain are a milder expression of a similar trouble.

A. Fraenkel (*Deutsch. Med. Woch.* 1887, No. 6, p. 101) has made a careful study of the necrobiotic processes which sometimes affect the upper air passages of typhoid patients. Wagner and Cohn had described a form of angina which they regarded as a specific manifestation of typhoid. Fraenkel insists, and with justice, that if this is a specific angina typhoid bacilli should be found in the lesions; whereas they never have been found. On the contrary, they are secondary infections with other organisms. He shows how exposed to secondary infections these parts are. These changes are much more of a character described by Eppinger as *necrosis epithelialis mykotica*, and the staphylococci are mainly to blame.

At the last Congress of French surgeons, in March, 1891, Panas spoke of a case of orbital angioma which of itself is rare, but which in this case presented features of unusual interest. The lesion had begun at the age of two, and under treatment had somewhat protruded. Vision remained good until the age of eight when the patient suffered from typhoid fever. She then presented a phlegmonous inflammation of the orbit, which necessited enucleation. He then found a small tumor, deeply seated, which contained pus. This pus was examined and found to contain typhoid bacilli, so that he had to deal with a spontaneous endo-infection of an angeioma by this specific bacillus.

At this last Congress of French surgeons, also, Panas reported that he had met with five or six cases of endo- or secondary infection consecutive to influenza.

Stern and Hirschler (*Wien. Medicin. Presse*, 1888, No. 28) have reported one case of suppurative parotitis following typhoid, in the pus from which both staphylococci and streptococci were found. Also one case of croupous pneumonia in a consumptive patient in whose sputum tubercle bacilli were found. Also a case of puerperal mixed infection, occurring nine days aft r confinement, along with high intermittent fever, with exudate around the ovaries. Seven weeks afterward the patient displayed a left-sided empyæma which perforated the lung three weeks later. Three days before this perforation streptococci and staphylococci were found in the blood, which must have been invaded from puerperal infection.

Hanot has collected four cases of orchitis during typhoid fever, one of which ran on to suppuration. Liebermeister alludes also to the same thing. It seems also to be a fact that at certain medical stations orchitis is known to follow on a fever whose nature is somewhat doubtful, some considering it remittant and others typhoid. It most often occurs during convalescence, and is often accompanied by rheumatic pains The same is true of ovaritis.

Neve, speaking of abscesses of soft tissue which occur as sequelæ of typhoid, alludes to a minute lesion often found in mesenteric glands, spleen and liver. This, which is of the nature of a localized cloudy swelling, he believes to be infective.

DIPHTHERIA.

Diphtheria belongs also to the maladies which may be accompanied or followed by severe complications in bones and joints. That it is frequently followed by abscess is so generally recognized as scarcely to call for comment here. In this place we intend to allude to those lesions which are produced, perhaps, primarily by the bacilli of this disease, or mainly secondarily by the common pyogenic and other cocci in the shape of mixed or secondary infections. Considering the well-known lymphoid character of the tonsils and neighboring adenoid tissue which is so universally affected in this disease, it is not difficult to trace a possible path of infection and one which is apparently more commonly followed than that originating in the intestinal canal, and discussed in previous captions. Here, again, from ignorance or failure to read correctly, too many of the joint affections consecutive to diphtheritic angina have been regarded as rheumatoid in origin. The thought comprised within this statement is not intended to be confused with another that may come at once to the reader's mind, that in many cases of genuine rheumatic trouble, or more commonly of gouty trouble, there appears to be a sympathetic infection of the throat or possibly in the muscles of the neck. It has been widely recognized that, after many of the more malignant forms of diphtheria have resulted fatally, multiple abscesses have been found in the liver, the spleen and the lungs, as well as in and around the bones. This would betoken a termination by true pyæmic processes, which yet have not been permitted time in which to produce a secondary crop of metastatic abscesses in the joints and other organs. No allusion is intended in this caption, either, to simple œdematous infiltration of the soft parts or limbs, by which a swelling may be produced in the neighborhood of certain joints, nor even to a simple serous effusion into the joints themselves. Such manifestations may be produced at almost any time as the result of the more pronounced forms of nephritis. These are not mixed infections in the sense in which we are using the term, although they cause many local appearances which might easily be mistaken for those of genuine idiopathic and rheumatic attack. There are undoubted cases on record where patients have succumbed to, or have recovered from a series of multiple abscesses in or around various joints, which perhaps were of a truly metastatic character, following closely upon, or occuring during attacks of diphtheria, whose pharyngeal symptoms varied in intensity in different cases. Schuller, in five different bodies of those dying of diphtheria, found various cocci in the serous effusions or fluid from the joints. ("Transactions of the German Congress of Surgeons, 1884, Vol. 13).

Fungous inflammation of joints as a sequel of diphtheria is not rare, as the experience of most physicians will show. As a rule, it runs an acute course, at least in the beginning, but usually terminates, after a fashion relatively favorable to the patient. Perhaps such cases are to be regarded as a conflagration by tubercle bacilli, permitted by the well-known lowering of vital resistance which diphtheria always produces.

Pauli, in the course of an epidemic of diptheria, observed twice out of twenty-seven cases a very rare exemplification of multiple arthritis which he attributed directly to the action of diphtheritic virus on the synovial membrane. One of the patients was a lad of fifteen, the other a child of thirteen. The inflammation involved nearly all of the joints, including even the temporo-maxillary and costo-sternal. Although both patients recovered the articular complication lasted for a long time. The clinical findings in that one of his cases in which one of the temporo-maxillary joints were involved, along with others, suggest to the writer the possible explanation of some of the complications of diphtheria and scarlatina, in which the source of the principal local infection is in intimate relation with this joint. While I have no data at hand to show that this is exactly the case, yet it is not difficult to understand how, from an infection of one of these joints, metastatic complications might very easily occur, to say nothing of the anchylosis of the jaw which is known to sometimes result.

SEPTIC ANGINA.

For some years certain authors have referred under this name to a complex pharyngeal disease which seems to lead so rapidly to a fatal result as to make us think that we have to deal in such cases with a veritable septic intoxication. Verneuil and Landouzy have reported interesting observations on this subject, and have remarked upon the inter-relations betwen these lesions and articular or renal symptoms. Lapersonne reports, for instance, the case of a man previously healthy who, fifteen days before the appearance of phlegmonous angina, had suffered from a large ulceration in one tonsil, and who evinced exophthalmus and severe cerebral symptoms. He died shortly after and the autopsy revealed the existence of a suppurative phlebitis of the ophthalmic veins and the dural sinuses. *Apropos* of the cases of angina which accompany albuminuric nephritis, Landouzy asks if the tonsils may not furnish a port of entry for such infection, since it is of course well-known that this complex sebaceous organ, developed upon a mucous basis, is in intimate relation with lymphoid tissue and lymphatic vessels. Other French writers have reported such cases as the following, for instance: A suppurative arthritis of the wrist consecutive to an infectious pharyngitis, which had been regarded at first as a case of glanders. Puncture revealed only the ordinary bacteria, and inoculations upon animals produced no septic lesion. Another case of very severe angina accompanied by high fever in a patient who some days later was seized with intense pain about the wrist, followed by signs of very severe local infection. A little later peculiar phenomena appeared about one knee. He fell into a typhoid condition, was delirious at night, and his condition gave rise to the greatest alarm. Free incisions were made, and antiseptic irrigation practiced,with good result.

It has happened to me in my own practice to see one case of very serious cynanche tonsillaris, with accompanying suppuration in and around the tonsil and pharynx, where we stood ready for hours to make tracheotomy for relief of threatened suffocation, in which an extensive abscess developed about one knee, with two smaller ones near the lower part of the leg. This was before pus had ever been studied bacterologically, so I can say nothing further about it than that it offers probably a case of secondary infection,

MUMPS.

The infectious character of mumps is probably not questioned to-day. Its contagious and epidemic characteristics compel its classification along with the general infectious diseases. Capitan and Charrin even claim to have cultivated its microbe, to which they ascribe specific properties, although their claim is not yet generally recognized. They have found it, in the blood and saliva, as a bacillus two to three micromillimeters long, very motile and capable of cultivation, but they cannot reproduce the disease with it.

In the course of this disease, as in that of other infectious diseases, we frequently observe various pathological manifestations, while orchitis, ovaritis, stomatitis, enlargement of the tonsils and spleen, and albuminuria are most commonly associated with it. Articular or peri-articular complications have been noted by several writers. Thus in 1850 Rilliet reported the case of two brothers whose attacks of mumps were rapidly followed by what he described as acute rheumatism. Later Begeron reported a case of bursitis of the præpatellar bursa. In 1877 Gailhard cited two cases; the first a soldier æt. 21, who had double parotitis on the right side, epididymitis with in tense headache, and arthralgia; the second a sailor whose ankles and wrists were seriously involved during convalescence from mumps. Jourdan watched an epidemic of mumps in a battalion of chasseurs. Four of them were, toward the end of the disease, seized with severe articular pains in various joints for which they asked their discharge from service. Boisset published under the term pseudo-rheumatism the case of a soldier recovering from a mild attack of the mumps, who, about the twelfth day, was seized with severe pains in many of the joints, which a little later seemed to localize themselves in the sheaths of the common extensor of the fingers, in the extensor of the index finger and the extensors of the thumb of the right hand. The tendons were also apparently involved, the pain was more severe at night and increased by pressure or movements. There was no particular change for eight days, then rapid amelioration for three days, after which relapse occurred. Hydrarthrosis of the knee also appeared; finally the patient completely recovered.

LECTURE X.

MIXED AND SECONDARY INFECTIONS.

(CONTINUED)

SYLLABUS.—Mixed and Secondary Infection Complicating Erysipelas; Lymphangitis; Variola; Cerebro-spinal meningitis; Infectious pseudo-rheumatism; Infectious endocarditis, Erythema multiforme; Tuberculosis; Glanders; Anthrax; Syphilis; Gonorrhœa; The puerperal state; Other genito-urinary lesions.

ERYSIPELAS.

AMONG the earliest authors to describe the supervention of rheumatoid inflammation during erysipelas, was Trousseau, who regarded them as agreeing in this respect that their symptoms were metastatic, and were, after a fashion, interchangeable. In other words, that the one could, as it were, take the place of the other, or that they could co-exist; and then he speaks of a young man suffering from facial erysipelas, who was suddenly seized with rheumatic pains, who had often suffered from the former, and who, since the accession of the latter had developed an endocardial murmur, most all of whose joints, even the smaller ones, were involved and who was a very sick man. As in the case of dysentery, the endeavor has been made to regard erysipelas as an external manifestation of rheumatism. Perroud was especially responsible for this view, and he found some reason for it in the frequent occurrence of a coincident cardiac affection; but this view has now no value, although it is well recognized that endocarditis is a frequent complication of erysipelas. That there is a form of rheumatoid arthritis consecutive to erysipelas we must accept, but it appears to have nothing except locality in common with a much more severe and disastrous joint lesion in the shape of pyarthrosis. It is impossible to disregard the biological fact that the specific parasitic agent in producing erysipelas, as in infectious endocarditis, is one of the well-known pyogenic streptococci. For a more definite reference to this organism and its proper position among other organisms, we must refer back to Lecture III. When we remember how common it is to have a superficial abscess or how, not infrequently, we have to deal with severer phlegmonous forms, we certainly ought to be genuinely surprised that so seldom we have to deal with the presence of pus in the bones or joints, or even in the nodes. For these cases we have scarcely to invoke the theory of a secondary or mixed infection, since we consider the streptococci of erysipelas of themselves sufficient to produce pus, although such is by no means their invariable action. Indeed the frequency with which positively distinct and undoubted manifestations of erysipelas occur, from which the specific organism can be readily cultivated, and yet without formation of a drop of discoverable pus, forms about the only argument in favor of a biological distinction between the streptococcus erysipelatis, and the streptococcus pyogenes.

Musgrave appears to have been the first to notice the coincidence between erysipelas and arthritis, and in 1709, in a work upon abnormal arthritism he mentions erysipelas as among the accidents which may determine this condition. Lorry speaks in the same sense. Joseph Frank mentions an arthritic erysipelas. Profeta classifies erysipelas among the symptomatic dermatoses of rheumatism and gout, and Pierre Frank, of Palermo, thought that suppressed gout might reappear in the form of different cutaneous affections, particularly in that of erysipelas. Of course all these views are now attributable to the ignorance of that age concerning the nature of the disease, which was then considered as an ordinary dermatitis.

While of course its infectious character is everywhere recognized to-day the history of the disease shows that its contagiousness was suspected by Lorry in 1777, and definitely and forever established by Velpeau and Trousseau.

It is only proper also to make a distinction between cases where there has been a direct extension from the skin to the underlying synovial membrane, these being analogous to those where the disease spreads from the scalp to the meninges, or from the skin to the peritoneum, and those implications of joints which are at a distance from the part involved in the cutaneous manifestation. For instance Despres has described the case of a patient who had undergone an operation for cataract subsequent to which a violent erysipelas of the face developed. In this case pus was found in remote joints. Lawrence, Avery and Velpeau have noted the same distinction, and Volkmann mentions multiple pyarthroses which he separates sharply from embolic pyaemia, since they lack the clinical features of chills, temperature curves and other signs which genuine pyæmic cases present. When the disease is the result of direct extension, the prognosis is better than when it is of the latter general character. During the last Franco-German war a large number of patients in the Berlin barracks who had suffered from gun-shot fractures were seized with erysipelas, in consequence of which many of them died, sometimes of the disease itself, sometimes of a final pneumonia. Among 130 of these well marked cases, pus was found five times in the interior of the joints, over which the erysipelatous inflammation had spread. When we remember the anatomical fact that the joint cavities are practically enormous lymph spaces, it will be less difficult to appreciate the course of events in such cases as these. In other words, we have to deal first probably with a serous arthritis while the infection with pyogenic cocci is the secondary result.

Such a case as the following reported by Breusing is quite suggestive: An old man suffered from fracture of the neck of the femur; after a while he developed an erysipelatous affection in the sacral region, which wandered down the left leg and in five days spread over the left knee; in twelve days he died. At the autopsy pus was found in this knee which connected with external bursae. Cultures made from the serous exudate taken from this same knee a week previous to the death proved to be pure cultures of Fehleisen's coccus.

In a clinical study concerning surgical infectious diseases, published in 1890 in Munich, by Fessler, he reports that an inoculation with a mixed culture of bacillus prodigiosus and streptococcus of erysipelas seems to produce more violent reaction upon the rabbit's ear than does the streptococcus alone, the reaction even proceeding to gangrene. It is not at all unlikely that some of the phlegmonous manifestations of erysipelas may be due to mixed infection after this fashion, although not necessarily with the bacillus spoken of here.

Lymphangitis.

Verneuil, in a memoir read before the Academy in 1878, reported five cases in which a lymphangitis of the lower limb was followed by an arthritis or a hydrathosis of the knee. In one of these cases the collection of pus was so large and the phenomena so grave that amputation was proposed but refused. Drainage was then made, with antiseptic injections, but the patient died in a very short time, and at the autopsy the cartilages were found destroyed and the spongy bone saturated with pus. This patient entered the hospital suffering from some undetermined fibromatous condition with a gangrenous area on the back of the foot. Perhaps this is scarcely a typical case of its kind, since septic organisms had ready access from the necrotic area. On the other hand it is almost impossible to conceive of a lymphangitis not of microbic origin. Consequently it may stand, after all, as a specimen of its class.

Variola.

But little is said in recent literature concerning the development of serious lesions of a surgical character consecutive to small-pox. A large amount of what little has appeared upon it is met with in the writers of the early part of this century, about the latest distinct contribution to the subject being that of Bidder, relative to an epidemic of small-pox in Halle during 1870 and 1871, as the result of which several patients with purulent collections in and about the joints presented themselves in Volkmann's clinic. Here again, as was so universal, we find the same confusion of all obscure forms of joint trouble with rheumatic affections. Thus Brouardel mentions that he saw rheumatoid affections five times among 389 patients; they appeared during the stage of desquamation and he was able to convince himself that there was no pus present. An observation of Friedheim's, made during 1885, is of very great value. It concerns a boy, æt. 12, who was seized with small-pox, who, after it had disappeared, complained of violent pains and disability of the left arm and of the left hip. Even upon the next day it appeared as if the head of the humerus could be almost lifted out of its socket; there was no fluctuation; the left leg was strongly flexed upon the abdomen, and adducted. The trochanter was 4 cc above its normal position. Extension was applied. The spontaneous dislocation was reduced and the patient finally recovered.

The only joint manifestations of interest during the course of this disease are the arthropathies. Thus Rilliet and Barthez say that they have often observed a circumscribed phlegmasia about the joints, which were swollen, red and painful, resembling rheumatism in many respects. The inflammation involves one joint and passes rapidly to another, or it involves several at the same time, and then disappears after a few days, leaving no trace behind. Brouardel is rather of the opinion that this is a genuine rheumatism, since the periosteum of the long bones is often involved, and since endocarditis sometimes occurs. But a true suppurative arthritis involving several joints is common, and sometimes, according to Bidder, fragments of bone are evacuated, after which the joint recovers. These accidents occur most commonly during the period of drying up of the pustules or during convalescence.

Concerning the nature of these sequelæ Rilliet and Barthez think it is impossible to see, in the multiplicity of these phlegmonous processes and their dissemination, even in their metastatic character, anything less then a general cause such as numerous French writers speak of as a purulent diathesis. Bidder observed suppurating joints five times in young children, suffering from variola, and in each there was coincident formation of abscesses. Bourcy rejects the theories of metastasis, and believes in a variolous intoxication as the determining cause.

Trousseau mentioned years ago that in cases of small-pox, joint inflammations apparently very easily took on a purulent character, and was of opinion that this peculiar disposition to suppuration was the result of a specific action. He distinguished between multiple joint inflammations of this character and true metastatic pyæmia, which latter begins usually on the 9th to the 14th day and at a time when the skin is beset with pustules. True pyæmia according to Curschmann (Ziemssen's *Hand-book*) appears to be a very rare complication. Two very instructive cases of purulent arthritis following small-pox were reported respectively by Guersant in 1834 and Thomas in 1835. The former case was that of a lad of sixteen, who having just recovered from pneumonia, was seized with small-pox. One joint after another was involved, and a severe conjunctivitis was added to his other troubles. Rigors set in with extreme emaciation and diarrhœa. He died four weeks after, and upon dissection pus was found in most of the affected joints as well as in the tendon sheaths. The second case was that of a young man, æt. 21, who on the 28th day of an attack of dysentery developed variola. He also died with multiple pyarthroses, and pus was found in numerous joints. The cases reported by Bidder appeared mostly as periarticular rather than intra-articular collections of pus, and partook somewhat of the character of suppurative epiphysitis. He is rather of the view that the deeper lesion in such cases is a result of extension from the overlying skin, inasmuch as the joints whose cavities are nearest the surface are mostly affected. The occurrence of acute abscesses in the bones has also been noted, especially by H. Fischer. When we consider the mass of pustules which cases of this character present, we have reason to wonder that suppuration in deeper tissues is not the rule rather than the exception. Guttman found pyogenic staphylococci in the contents of the variolous pustules and vesicles as well. Garré succeeded in cultivating streptococci from the juices of various organs, from which it appears that pyogenic microbes are carried in the blood to all parts of the body, and we are compelled to fall back on the view that, as a rule, the tissues even when poisoned with this disease do not furnish favorable soil for their development.

Neve, speaking of the confluent variety of small-pox, says that the formation of boils and abscesses is common, and that it is not strange that, in a suppurative disease like variola, symptoms of a pyæmic nature should occur. Inasmuch as we do not yet know the specific germ of small-pox, we are unable to state whether it possesses pyogenic properties, or whether the pustules which characterize the disease are the result of mixed infection or not. Presuming that the latter is in many instances the case, it is easy to see how the poison may be absorbed by the lymphatics, and passed on to the small veins, from which it may be scattered far and wide; and undoubtedly many of the abscesses met with in this disease, as well as the cases of necrosis, may be explained as metastatic phenomena. Of thirty-six cases of bone and joint disease commented on by Neve, four were cases of alveolar necrosis, twenty-six suffered from joint disease, and in twelve one or more epiphyses were affected. The upper extremity was the more commonly involved, which he explains by the fact that most of these patients were children, and that little children use their arms more than they do their legs.

The occurrence of orchitis has been noticed in various febrile affections. Velpeau and Berand have described a form developed during small-pox, and Trousseau speaks of it at some length.

Cerebro-Spinal Meningitis.

It seems to be fairly well established now that this disease, certainly its epidemic form, is of microbic origin, and this being the case we need not be surprised to find evidences of secondary infection, providing only that patients live long enough to develop them. As a rule, however, death occurs with such rapidity that time for secondary symptoms is scarcely offered. Nevertheless, the studies of such authors as Grisolle, Laveran and others show that we do have at least articular complications, and that from the fifth to the eleventh day, if life persist so long, acute arthritis may occur, often with suppuration. The larger joints are those commonly attacked, including probably those of the vertebral column. In this fluid according to Cornil and Babes, bacteria are always found.

INFECTIOUS PSEUDO-RHEUMATISM.

This forms a chapter in the monograph of Lapersonne, who describes under this term certain cases of usually multiple synovitis or arthritis whose prime cause it is impossible to discover. They come on sometimes as the result of fatigue following trifling injury or burn, sometimes after a sore throat, even mild, and sometimes without any appreciable cause. They are preceded or accompanied by constitutional symptoms, which are sometimes mild like nausea and malaise, and sometimes violent like delirium, severe headache, etc. Locally these cases present two forms, the pyretic and the apyretic. Under this term he includes quite a number of fatal cases in which, upon autopsy, were found all the ordinary anatomical manifestations of an infectious disease. He insists upon their separation from typhoid fever, from ulcerative endocarditis, and above all from acute articular rheumatism.

INFECTIOUS ENDOCARDITIS.

Only within thirty years has the individuality of this disease been recognized. In the interval since Rokitanksy and Virchow dispersed all doubt as to the existence of acute ulcerations of the endocardium, numerous researches have been made, and the names of Pelvet, of Klebs and Weigert, of Prudden and Osler, along with a host of others, must always be prominent in the history of the subject. That the disease deserves the characterization often given to it of *malignant* is well known. It is, in fact, an infectious disease with especial localization in the heart, the term cardiac typhus, given to it by some, being very expressive. Although so often apparently spontaneous, it is in fact usually a secondary disease; in large measure it is a secondary infection. Its parasitic nature is of course placed beyond a doubt, although we have learned that the organisms which may cause it are the common and well-known pyogenic cocci, their virulence in these cases being as intense as in cases of infectious osteo-myelitis. When we consider the peculiar location of the lesion in this disease, we shall have no difficulty in appreciating the readiness with which metastatic complications may arise; the wonder is rather that they do not always occur. The arthritic manifestations are usually of a pyæmic character, although even at the beginning, as Trousseau pointed out, there are frequently severe joint pains. Abscesses may form very rapidly, while around the joints there occurs a diffused œdema which is simply another sign of the intensity of the trouble.

The specific or infectious form of endocarditis is perhaps to be separated from a non-septic form of acute endocarditis, which is perhaps of acute rheumatic origin, in the course of which we have, however, perhaps at the same time, multiple hæmorrhages and articular effusions, which latter, according to Strümpell, are of a serous and not a purulent character.

ERYTHEMA NODOSUM SEU MULTIFORME.

By some writers this has been classed among the infectious diseases. Trousseau ranked it among the eruptive fevers. Hardy considered it a manifestation by itself, to be compared with post-scarlatinal rheumatism. Other French writers consider it as a specific disease whose external expression is the eruption. In 1886 Villemin reported to the Academy of Medicine eleven cases of so-called infectious erythema. In his fourth case he had noticed severe arthritic manifestations in a number of joints, which he considered as connected with the primary disease. The writer has had no experience with complications of this character in this somewhat rare disease. A case occurring recently in his practice, however, is worthy of mention in this connection. A middle aged man of rather free habits, was operated on for numerous and deep strictures of small caliber. The first week after the operation passed without especial incident. With the beginning of the second there appeared the multiform manifestations of this condition, which seemed to be exaggerated by each of two successive soundings with a large sized steel sound. Finally the eruption took on a nodose character in severe form and gave rise to some apprehension for a few days. There were no joint complications in this case, and the erythema itself must be considered as secondary to the surgical intervention. I find that dermatologists speak of the occasional supervention of this disease after surgical operation or irritation. Nevertheless, if it be in any sense a specific disease, one can see how from an infected and unhealthy urethra, abundant opportunity for the entrance of the germs is offered.

Tuberculosis.

So much has appeared of late on the matter of tuberculosis in its surgical and pathological relations, that the space assigned to it in these lectures will intentionally be made small as compared to its importance. To only two or three phases of the subject shall I invite your attention. I desire to make it clear, however, that tubercular mixed infection may be of two kinds: First a condition in which we have a secondary pyogenic infection of a primary tuberculous focus, and, second, a tuberculous infection of a previously healthy area, or of a wound whether healing kindly or suppurating. I do not know that anywhere proper and distinctive attention has been called to these two manifestations. Instances of each of them must be extremely common, and I need but to illustrate them to you to be sufficiently explicit.

Let us take first a primary tubercular infection in the lungs. Lung texture previously normal has become infected, and in consequence is studded with few or many miliary tubercles which later coalesce and form what we call a tubercular nodule. Certain physical signs indicate this state of affairs. A little later we have a secondary infection of this nodule by pyogenic and saprophytic organisms, the result of their action being the formation of an abscess or as we say a lung cavity. This abscess may be miliary in size, or may produce a cavity as large as a hen's egg. This occurs in the lungs; its counterpart may be met with in any of the viscera or in the glandular system.

Take now a more distinctively surgical view of the same character of lesion. From some cause which it is not necessary here to discuss, the cancellous tissue in the neighborhood of an epiphysis becomes infected, miliary tubercles form, and there results that peculiar proliferation of tissue which the Germans call fungoid, and which we may speak of as infectious granuloma. As this increases in amount it erodes away other tissues and so advances in other directions, now perforating a joint, now boring through the periosteum and soft parts to appear at the surface by a livid purple area, after which complete perforation of the skin may follow; or tunneling beneath strong fasciæ, extending always in amount, and causing irritative hyperplasia in its vicinity, whose combined external manifestations are constituted by more or less swelling. It is frequently possible to find or to cut into such tissue at a time when it shall present nothing more than is described above. Up to this point we have a primary tuberculous lesion, but the clinical or pathological picture is liable to change at any time, and in addition to the above we then have all the added signs and symptoms of rapid or slow suppuration; all of which means a secondary infection by pyogenic or putrefactive organisms, while in the pus which may be later evacuated from such a focus tubercular bacilli may or may not be found, this depending in large measure on whether the collection be recent or old. These are illustrations of the first form of tubercular mixed infection.

Illustrations of the second are, perhaps, a little less familiar to those not engaged in surgical practice. Let me adduce a few illustrations.

A child originally healthy suffers from scarlatina. As a consequence of this he has purulent otitis with destruction of the membrana tympani, and exposure of the cavity of the middle ear to the outer world. The case goes on for an indefinite time as one of this character, when, later, tubercular infection takes place, in consequence of which we have specific caries of the bone with perhaps tubercular meningitis and death. In this case we might legitimately speak of the tubercular feature as constituting a tertiary infection.

Again, it is well known that dental caries is due to the specific action of several forms of micro-organisms, whose biology and properties have been illustrated by Prof. W. D. Miller. A tooth, which has been more or less destroyed by such agencies, permits a secondary tubercular infection to take place, more probably around it than through it, in consequence of which we have the well-known enlargement, always tubercular, of the cervical or sub-maxilary lymph nodes, in whose case again a tertiary infection occurs, this third time with pyogenic organisms, and now we have an abscess in the neck.

Again, a patient suffering from secondary or tertiary syphilis develops specific ulcerations in the nose or mouth. It is very possible for him to suffer from tubercular infections of these lesions before they heal, in such a fashion that he may recover from the syphilitic while being still contaminated by a tubercular lesion. In some such way as this undoubtedly many cases of combined syphilis and tuberculosis do occur.

Once more, let me quote a recent case of my own as serving as an excellent example: A strong and perfectly healthy man of excellent antecedents sustained a railroad injury of such a character that I was compelled to make a resection of the elbow, and the laceration of tissues was such that it was impossible to so perform it as to get recovery without necessity for granulation and consequent discharge of puruloid material. Necessity compelled the placing of this man in a small ward where were several other patients who were suffering from tuberculosis. This wound made rapid and favorable progress for some three weeks, when suddenly its aspect changed, its granulations became œdematous and it took on every aspect of a tuberculous ulcer. I deliberately watched it for a little while, and then made a second operation which comprised a scraping out of all infected tissue and the restitution of the parts to an aseptic condition. He was then sent out of the hospital and made rapid and complete recovery. Examination of the suspicious tissue removed showed tubercular bacilli present.

Another case, is that of a perfectly healthy young lady, who suffered from anchylosis of one elbow due to severe inflammation some years previously. Her physical condition and constitutional appearance left nothing to be desired in this direction. I resected her elbow, and the wound completely healed with a very little suppuration, to subsequently re-open at two points and display every local evidence of tubercular disease. In her case I cannot trace the source of the infection; in the previous case I can.

But why repeat, in what must be wearisome detail, examples of what everyone sees daily, though he may not attach sufficient importance to, or see the facts in their complete illumination. For my own part this topic of mixed and secondary infections consecutive to tuberculosis is perhaps the most important touched upon in this list because, largely, it is the most common. When I look over my own case books I find that from 20% to 25% of my cases concern this protean malady in its surgical relations. And others, like König, for instance, report that nearly 35% of their clinic cases are of the same nature. Do not such figures give it an overwhelming importance? And nevertheless are not the few instances which I have adduced as illustrative as a larger number?

Inasmuch then as I aim in these lectures only to be suggestive and illustrative, realizing that the time at hand permits nothing more, I must pass on; stopping only to remind you that the bones and joints are so freely spoken of during these remarks for the double reason that they afford as good examples of such lesions as any parts, and because they so especially interest the surgeons.

GLANDERS.

Clinical experience, especially that of veterinary surgeons, leaves no doubt as to the articular or secondary complications of this disease, whose contagious character has been recognized since the beginning of this century. Since the contagious nature of the disease was proved a few writers have insisted, and with reason, upon the occurrence of articular complications, and Bonnet in his treatise has given a characteristic example. Elliotson has noted the presence of pus within the knee, and several times the knee, hip, shoulder and elbow have been found involved. Suppurative tendo-synovitis has also been met with, especially underneath infected skin. These complications are more common after acute glanders than after the other forms. A genuine polyarthritis much like that of acute rheumatism, not going on to suppuration, has also been observed. These are all secondary infections, save possibly the last named.

ANTHRAX.

If we are to accept without question the opinion of Davaine and Pasteur, articular manifestations do occur in the course of this essentially infectious disease, although they are certainly rare; but we fail to find report of a single case where this is established without a doubt. A case quite suggestive, however, is reported by Chassaignac in his treatise on suppuration. It concerns the case of a young man, æt. 34, previously well, who contracted malignant pustule from the carcass of a sheep. Multiple pustules appeared upon the forearm and hand, and for their relief repeated cauterizations with the actual cautery were practiced. A little later swelling and elastic tension were observed upon the lateral aspect of the trunk, and there were fever, general malaise and peculiar pains about the joints, which latter swelled and acted as if affected with acute rheumatism. The patient made a slow recovery without secondary suppurations. Bollinger also has described certain cases of about the same character, from which it seems to me that the occurrence of mixed, if not secondary, infection is possible in these cases, although very rare.

SYPHILIS.

Syphilis stands in a somewhat peculiar position in this list of diseases since its manifestations which concern us here are usually connected with that form of neoplasm which is practically an infectious granuloma. Of course, the syphilitic patient by virtue of whatever cachexia he may manifest is the more liable to suppuration on slight provocation than the healthy individual. Furthermore, by virtue of the many ulcerated lesions which these patients present, the path for secondary and pyogenic infection is widely opened. Of course, too, we are yet ignorant of the infectious agent in this disease. So far as we now know, however, there is no clinical fact leading us to believe that this agent, whatever it may be, can ever be pyogenic when uncontaminated. In this respect it appears to differ from the tubercle bacillus, since abscess formation and breaking down are common in syphilitic and tubercular gummata alike, and there is every reason to think that the former are invariably, and the latter, at least most commonly, the result of mixed infection with pyogenic or perhaps saprophytic organisms.

As far as the joints are concerned it is not often, at least, that we have a true syphilitic arthritis, and a suppurating joint in an active case of syphilis must probably always be due to mixed infection. A hundred years ago John Hunter declared that he had never seen constitutional syphilis attack the articulations, and this was at a time when venereal diseases were sadly confounded.

On the other hand, in 1853 Richet claimed that syphilis alone could provoke synovitis and articular ostitis in subjects who presented no sign of scrofula. Still later Chomel spoke of hydrarthosis and hyperostosis of joint-ends as exceedingly rare manifestations of syphilis; but the infectious arthritides of syphilis were well treated of by Lancereau, after him by Fournier; and still later by Schüller, Volkmann, Mracek and others. But the non-suppurating lesions of late syphilis have no interest for us here, and we must close this short reference to the subject with the repetition of the statement that suppuration in these cases whether occurring in the brain, in the liver, in the epididymis or in joint cavities, is always the result of a mixed or secondary infection.

GONORRHŒA.

This disease belongs among those infectious processes which often give rise to joint inflammation as well as disturbance in the bones.* Its most common arthritic complication is, perhaps, the most frequent sequel of any that have been noted among the infectious diseases. In time past the French authors have made a very determined effort to group this disease among those of constitutional character. How earnestly they have worked in this direction may be seen in the writings of a large number; for instance, Pidoux has endeavered to show that gonorrhœa is a constitutional disease because of the pallor and facial expression, the rapid emaciation, the discoloration of the skin, occasionally noted, and other such insignificant features.

That there is in these cases a disturbance of the general system, or a sympathetic affection of functions, may be easily granted; but the endeavor to show the disease is *per se* of other than local character finds now-a-days very few if any sympathizers. Its last claim to this regard has been taken away from it by Neisser's discovery of a specific micro-organism which is capable of attacking only a very few mucous membranes. That arthritis is by no means the only surgical sequel is shown by the occurrence of such remote and inexplicable disturbances as iritis, which may occur without a secondary affection of the conjunctiva, while a form of conjunctivitis is known which does not partake of the purulent character. According to statistics presented by Nolen, 116 cases of gonorrhœal arthritis were accompanied by a conjunctivitis of the lids and bulb, or serous iritis, or by both. That some constitutions are much more easily affected than others is as true of this disease as of every other infection, but we are by no means prepared to accept that which the French have spoken of as the blennorrhagic diathesis.

The relations between blenorrhœa and gout or rheumatism were perhaps first alluded to about a century ago by Swediaur and Hunter, or even before them by Baglivi. The school of the Midi, the works of Ricord, of Cullerier and even of Velpeau, put the question upon a scientific basis, while the articles of Grisole, Ravel, and especially the chapter which Bonnet devoted to it in his work on the Joints, gave the topic an indentity of its own which has still later assumed yet greater proportions.

Literature concerning the gonorrhœal joint complications is most extensive, and the conflict of opinion concerning their character has been at times almost fierce. Nolen, for instance, studying the cases above referred to, 116 in number, takes the ground that there is no reason why this affection should be separated from polyarticular rheumatism, and there being no reason why a rheumatic individual may not suffer from the local disease, one may appreciate how up to a certain point it is possible to have something that might be termed gonorrhœal rheumatism; but that the disease usually alluded to under this name has something in it essentially different from rheumatism pure and simple, is definitely proven by such a discovery as perhaps Petrone was the first to make, viz: of Neisser's gonococcus in the joint fluids from such a case. The arthritic complications of gonorrhœa, as of most of the infectious diseases, comprise a trifling serous effusion, a catarrhal form and a genuine purulent form. In Nolen's cases he found arthralgia seven times, hydrarthrosis twelve times, serous synovitis sixty-four times, a purulent condition twice and arthritis deformans six times. These joint complications occur usually in younger patients, æt. from 20 to 30, and almost always in men. Only urethral or vaginal discharges lead to the complication, balanitis and posthitis never. Some authorities take the ground that arthritis never occurs in men unless the membranous portion has been involved; also, and I think with reason, that only the truly specific forms of blenorrhœa are likely to be followed by these results. One peculiarity seems to separate these troubles from the essentially rheumatic, and that is their great tendency to recurrence. Volkmann saw one individual who had joint complications after each one of seven local attacks. Frerichs even goes so far as to say that this commonly harmless disease may lead to death, but death as it were of a suicidal character. Joint symptoms set in most commonly during the second week, although sometimes not until all local symptoms have disappeared. The true arthralgias are often complicated with equally painful myalgias and ostealgias. The knee and the ankle are most commonly involved. Sometimes we have such a polyarthritis as to constitute a verisimilitude to a true rheumatic attack. Occasionally even the tendon sheaths and the bursæ take part in the disturbance, and to tenderness and sensitiveness in the tendons is added a swelling of the bursæ.

More serious and lasting disturbance than a temporary arthritis is by no means unknown. Complete anchylosis is rare, but painful joints whose function is long disturbed are common. Trendelenburg had recently to resect an anchylosed elbow thus stiffened, and he mentions a case from Langenbeck's clinic in which most of the joints, even these of the vertebrae, had become anchylosed to an extraordinary extent. With mere serous effusions, although they constitute a majority of these cases, we have in this place nothing special to do, but as already seen a true catarrhal inflammation is sometimes met with. Whether here we have to do with an unusual manifestation of activity on the part of the gonococci, or whether with a mixed infection, it has been in time past difficult to state; but as remarked in Lecture III, Neisser's diplococci are not known to have by themselves any pyogenic power. This would appear to be proven by a series of observations like that of Petrone, which have been repeated by numerous others, myself included. In the clear or almost clear sero-fibrinous effusion we have found these diplococci, yet never any pus unless other organisms were present. On the contrary when pus has been found other organisms are always present, *i. e.*, staphylococci and streptococci. There is reason to think that this is the case even in the urethra, which is never; at least in individuals subject to infection, free from the common pyogenic forms. In the seropurulent forms of joint effusion, we have apparently to deal with an infected fluid quite similar to that existing in a case of sero-purulent pleuritic effusion, which is capable of absorption, at least of the fluid portion, with death of the active organisms, and without serious damage to the enclosing membrane. But we have a more distinctly purulent form than this in which one or more joints fill up with clear pus. If this form be monarticular the patient may recover with function very seriously impaired or totally lost; if polyarticular it is usually fatal, the case then being indistinguishable from one of true pyæmia. One such case I reported in some detail in the *Journal of Cutaneous and Venereal Diseases* for December, 1888, and Nolen refers to four similar cases. Fournier reports a pyarthrosis of the elbow, which ended fatally, and Eisenmann and König each saw a case in which a purulent gonitis led to death from pyæmia. Holst treated a case in which an immense effusion in the knee joint disappeared for the most part by absorption, but brought about the pyæmic condition to which the patient succumbed eleven weeks after. Prichard incised an immense abscess on the outer side of the thigh, which was the result of a perforation of an empyema of the knee and had later to amputate the thigh. Wyschemirski also observed a polyarticular form of post-gonorrheal joint empyema which ended fatally. In the pus from one elbow Neisser's gonococci were recognized with the other cocci.

These various views have necessarily met with numerous unbelievers, many of whom have charged that the microbes of the articular fluid have about them nothing specific, and that their discovery depends in large measure upon the time at which the fluid is withdrawn for examination. As a matter of fact, however, Kammerer has found them, and Bousquet, in 1885, demonstrated in the liquid from a sterno-clavicular joint thus affected, the specific cocci of Neisser.

With reference to the occurrence of gonococci in joint fluid, the true position to-day is, as nearly as we can arrive at it, as follows:

Neisser's cocci may be found in the joint fluid in any post-gonorrhœal synovitis, though they are not necessarily always found. They are regarded by Fraenkel as the etiological agents in producing serous iritis, and if he be correct they would appear by themselves to have the property of provoking only serous or sero-fibrinous effusions. Careful bacteriological investigations of fluid taken from the joints involved in a true rheumatic inflammation fail to reveal any organism at all; but so soon as in either case we find pus, we find also the truly pyogenic organisms. Furthermore, in all cases of non-specific urethritis in which Neisser's cocci are not found, and with which they have nothing to do, we have no tendency, so far as known, to joint complications. In other words post-gonorrhœal arthritis may be due to the specific cause discovered by Neisser, though just how we do not know. Whereas whenever pus be present it is, accurately speaking, a secondary infection. It is no more difficult to understand how the pyogenic organisms may travel from the urethra to the synovial membrane, than how the gonococcus finds its own way thither. Explanation of this fact does not seem to have as yet been furnished, and if a monarticular form of either may occur, why not a polyarticular as well? The explanation of the pyæmia arising from urethral and peri-urethral infection requires nothing more than the occurrence of a local phlebitis, septic thrombi from which can easily produce the whole disturbance. That this is not excessively rare, in one form or other, is shown by the frequency with which writers have alluded to such complications as endocarditis and pericarditis.

Participation of the osseous system in post-gonorrhœal cases is much more rare, in fact only two authors have alluded to them, Petrone and Fournier. The latter has described a form which corresponds very well with the periosteal complications observed after typhoid and influenza. He speaks of extremely sensitive swellings of the periosteum which last two or three weeks, and terminate, ordinarily, by resolution, although possibly by abscess. They are met with most commonly where the bones lie subcutaneously. Aside from such abscesses as may be met with in the bones following a true pyæmic complication, I am not aware that bone abscess or acute osteomyelitis has been noted.

So far as purulent arthritis is concerned, numerous reports show the extent of the destruction which may follow. Thus Prichard was compelled to amputate a thigh, while Eisenmann lost a patient from general pyæmia after a manner quite similar to that in my own case elsewhere alluded to. Landouzy has reported the following remarkable case: A female, æt. 17, suffering from gonorrhœa, was attacked with most severe pain in the shoulder and right sterno-clavicular joint. Both joints were intensely swollen and extremely sensitive to pressure or movement, while fluctuation was well marked. A few days after her admission to the hospital there occurred a synovitis of the right peritoneal tendons within their sheaths with contracture of the foot. The joints were punctured, and the patient finally recovered, but with most marked secondary atrophy of the muscles of the leg and those of the thorax and shoulder on that side.

This view that certain individuals produce pus with less provocation than do others was for a time made a seductive one by the talent of Lasegue. According to this view gonorrhœal rheumatism is a form of pyogenic rheumatism, and the joint lesion is an expression of an attenuated or mitigated pyæmia. This view was adopted by Guerin, and was defended by such English writers as Paget, Holmes and Barwell, and within ten years by Talamon. Another view somewhat similar was that during an attack of septic urethritis the patient suffered from a transient diathesis such as all individuals with genito-urinary diseases manifest, or a cachexia resembling that of syphilis, in the course of which not only the joints but the viscera, the whole economic system in fact, were most susceptible. It was supposed to be somewhat analogous to that which has been observed during scarlatina. This view was defended especially by Loraine.

The visceral complications of gonorrhœa are less often alluded to, but are unmistakable. Nolen found cardiac lesions in 15 out of 116 cases of gonorrhœal arthritis, and analogous effects have been reported by Peter, Fournier and by others. Leloir has reported, for instance, a case of acute pericarditis in connection with a case of gonorrhœa in a young man. The case was very severe and was accompanied with intense pain in one knee, along with which, however, there was very little swelling in the joint. Of late several French theses have appeared bearing on the subject of cardiac complications of gonorrhœa. For instance Morel has reported several cases of acute pericarditis and endocarditis accompanied by all the serious disturbances characterizing these complaints, as well as severe joint complications, and his paper is well worth careful reading. He comes to the following conclusions: First, that gonorrhœa can be complicated by inflammation of the serous membranes of the heart as well as of the joints; second, that so-called gonorrhœal rheumatism, like the common rheumatism, may affect the heart even at the outset; third, that certain septicæmic accidents may give rise to these cardiac complications; fourth, that these latter may be very rapid and terminate fatally, although more commonly they are the causes of certain chronic lesions; fifth, that the treatment consists in first curing the gonorrhœa, and then combating by common measures the complications.

So also Marby, in a long paper on blennorhagic endocarditis has reported a number of cases, and has drawn conclusions which do not differ materially from those already alluded to. Most of his cases were observed in the service of Poucet.

Gluzinski has diligently studied the ætiology of post-gonorrhœal endocarditis and recurring pericarditis of which he has brought together thirty-one cases. He appears to see a relationship between intensity of the original gonorrhœal process, and that of the cardiac symptoms, and he lays great stress on the difficulty of deciding whether these cases are a genuine mixed infection or a truly specific one.

It would seem that these cases of complications of gonorrhœa are to be widely separated from certain disastrous surgical sequelæ of operations on the urethra made necessary by lesions of long standing. I know, for instance, of a man who had an old and somewhat deep stricture of medium calibre, upon whom a sound was passed without causing extensive pain or any alarming sign at the time, yet that night he was seized with a severe chill, and died within a week of some positively septic condition. Such cases as this, and many similar may be found in surgical literature, are undoubtedly to be explained by a minute lesion of the mucous membrane with infection of the exposed raw tissue by one or more of the forms of pathogenic and septic organisms, which abound in the urethra under such circumstances, as is well know to all who have studied it bacteriologically. To such infection succeeds septic phlebitis of the peri-urethral and peri-prostatic vessels, than which nothing can be more favorable for purposes of general infection. Such cases as these are to be studied as secondary infection after a fashion, but not after just the fashion to which I am devoting myself at present.

THE PUERPERAL STATE.

Inasmuch as no essential pathological distinction can be made between the various conditions included underthe name purperal fever, and septic complications of any ordinary wound or injury, it is impossible to make any minute distinction between the various infections which may follow this dreadful malady. Puerperal fever is essentialy either a post-puerperal septicæmia or pyæmia, and inasmuch as the septic infection in one case follows local channels, or in the other assumes the metastatic rôle when we have to deal virtually with the same lesions as those in ordinary surgical cases, and inasmuch as both streptococci and staphylococci are concerned in these cases, because they are in fact generally mixed or double infections, so the lesions display the characteristic disturbances of the well known parasitic inroads. Whether these be in the nature of phlegmasia alba dolens, an abscess during the establishment of lactation, a post-puerperal peritonitis, or the development of abscesses in various parts of the body, the active part played by these organisms is always the same and about the only perplexing problem in the matter is the reason why infection takes place slowly in some cases and rapidly in others, or why the programme is so diversified.

I remember, for instance, the case of a young primipara whom I had to see a number of times in consultation, who developed abscesses in various parts of the body, in the bones us well as about some of the joints, the neighborhood of certain epiphyses being especially frequently attacked, who nevertheless lived for several months, and finally succumbed to the exhaustion consequent upon the duration of her trouble. In the pus from one of these abscesses, I discovered both forms above alluded to, and as I think over the case now only wonder that she could have lived so long. She developed also an endocarditis of considerable severity, and this helped to terminate her life. Of course, in such a case there was no difficuly in accounting for the presence of pyogenic organisms at the time of her delivery and the primary path of infection in such cases is too well known to call for remark here. Cases so chronic as hers, however, are infrequent, and perhaps justify the prominence given to them here.

Other Genito-Urinary Lesions.

That recent gonorrhœa is by no means the only disease of the genito-urinary system by which mixed or secondary infection can be brought about will be plain upon a little furthur consideration. It is well known that abscesses in the kidneys are frequently met with which cannot be accounted for by trouble extending upward from below. While it may be hard to explain many of these cases, certainly many of them find explanation in the physiological fact that the kidneys are excretory organs, whose function is sometimes called into play for the purpose of eliminating certain pathological organisms which have gained access to the circulation. Certain other of these abscesses are due to tubercular disease in these organs, and some of these consequently are mixed while others are secondary infections.

It is also well known that normal urine when extravasated or injected is capable of resorption without provoking serious disturbance. On the other hand when overloaded with the various morbific and toxic products pertaining to many diseased conditions, it is positively toxic and if it contain, from any source, pathogenic organisms, it may, if it escape from its accustomed conduits or reservoirs, produce intense local or fatal general disturbance. Pyo-nephrosis, for instance, is by no means always a primary disturbance since it is often an evidence of secondary infection, which it may reproduce, or even cause a tertiary infection. Moreover, the results of abnormal escape of unhealthy urine, as from a ruptured bladder or urethra, are not only well known but must be regarded in the light of secondary or mixed infections. That the tissues badly bear the brunt of such infection is largely due to the intensity or virulence of the local infection. When time offers abscesses will often be met with in the joints or elsewhere about the body.

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